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Physicochemical interactions between drugs and superdisintegrants

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Abstract

We have evaluated the interactions between superdisintegrants and drugs with different physicochemical characteristics, which may affect the in-vivo absorption e.g. after mucosal administration. The binding of sodium salicylate, naproxen, methyl hydroxybenzoate (methylparaben), ethyl hydroxybenzoate (ethylparaben), propyl hydroxybenzoate (propylparaben), atenolol, alprenolol, diphenhydramine, verapamil, amitriptyline and cetylpyridinium chloride monohydrate (CPC) to different superdisintegrants (sodium starch glycolate (SSG), croscarmellose sodium (CCS) and crospovidone) and one unsubstituted comparator (starch) was studied spectrophotometrically. An indication of the in-vivo effect was obtained by measuring the interactions at physiological salt concentrations. SSG was investigated more thoroughly to obtain release profiles and correlation between binding and ionic strength. The results showed that the main interactions with the anionic hydrogels formed by SSG and CCS were caused by ion exchange, whereas the neutral crospovidone exhibited lipophilic interactions with the non-ionic substances. The effect of increased ionic strength was most pronounced at low salt concentrations and the ion exchange interactions were almost completely eradicated at physiological conditions. The release profile of diphenhydramine was significantly affected by the addition of salt. It was thus concluded that the choice of buffer was of great importance for in-vitro experiments with ionic drugs. At physiological salt concentrations the interactions did not appear to be strong enough to influence the in-vivo bioavailability of any of the drug molecules.

Introduction

Superdisintegrants, such as croscarmellose sodium (CCS), crospovidone and sodium starch glycolate (SSG), are commonly used in solid formulations to decrease their disintegration time. Their ability to absorb water can also be employed to create mucoadhesive delivery systems in, for example, sublingual (Bredenberg et al 2003) and nasal (Fransén et al 2007) drug delivery. This recently developed delivery system for nasal administration consisted of interactive mixtures with SSG as carrier particles to which micronized particles of the active component were adhered during dry mixing (Fransén et al 2007). The concentration of superdisintegrant would be comparatively high in such delivery systems and the release of a drug substance could thus be substantially affected if it chemically interacted with the polymer. Interactions have been described between CCS and cationic drugs (Chien et al 1981; Hollenbeck et al 1983; Huang et al 2006). Also SSG was shown to interact with a weak base, whereas unsubstituted starch did not (Chien et al 1981). Both SSG and CCS form anionic hydrogels after water absorption (Figure 1), and so the binding of the substances could be explained by ion exchange and was diminished by increased ionic strength in the solution (Hollenbeck et al 1983). The oral bioavailability of the weakly basic drug phenylpropanolamine (norephedrine) was therefore unaffected by the addition of CCS in the formulation (Hollenbeck 1988). Binding should thus be of greater importance when water with lower ionic strength is used, for example during in-vitro release studies or during analysis, as reported by Huang et al (2006). However, if stronger interactions between the superdisintegrant and certain drug substances are formed that persist even at physiological salt concentrations or if a high amount of superdisintegrant is used, it may impede the in-vivo absorption.

It is well known that surfactants are prone to interact with polyelectrolytes (see the review by Hansson (2006)). In these systems, the interaction is amplified by a greater entropic gain

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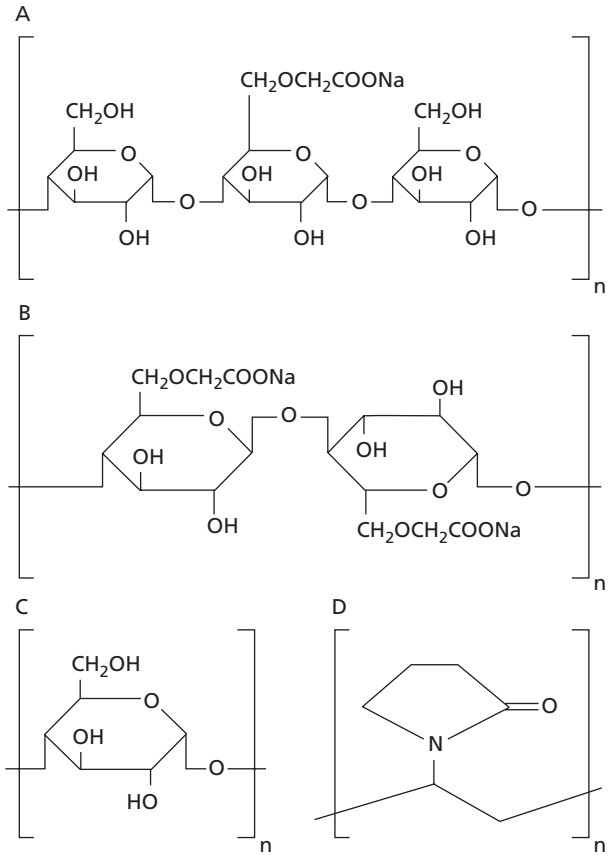

Figure 1 Simplified chemical structures of (A) SSG, (B) CCS, (C) PPS and (D) crospovidone. Redrawn from Rowe et al (2005).

than from simple ion exchange caused by aggregation of the surfactant inside the polyelectrolyte and shielding of the repelling forces between the polymer chains, which also causes the gel to shrink. The concentration of surfactant necessary for aggregation, i.e. the critical aggregation concentration (CAC), is generally very low but will increase with increased ionic strength as a cause of the smaller entropic gain upon the release of counter ions and the reduced effect of shielding of the charged polymer groups. Amphiphilic drug molecules will also associate to form micelles in solution, although with a more complicated association pattern (Attwood 1995) and generally at a higher concentration than the surfactants. Nevertheless, because the CAC is normally lower than the critical micelle concentration (CMC) there is a possibility that drug substances with a clear amphiphilic character could interact with the superdisintegrants to a greater extent than simply by ion exchange. If so happens, there is a risk that these interactions could not be eradicated by increased ionic strength.

The non-ionic polymer network in crospovidone (Figure 1) should not cause any interactions by ion exchange; yet, in this case lipophilic interactions may occur with amphiphilic or neutral molecules. As higher ionic strength amplifies lipophilic interactions these may even be more pronounced in-vivo than during in-vitro experiments.

The aim of this investigation was to evaluate which substance characteristics were of importance for interaction with the superdisintegrants SSG, CCS and crospovidone. Partly pregelatinized maize starch (PPS) was included in the study as an unsubstituted comparator to the two anionic polysaccharides. The interactions were studied at physiological salt concentrations to see if they could affect the in-vivo absorption.

Materials and Methods

Materials

Croscarmellose sodium (CCS; Ac-Di-Sol) was a gift from FMC BioPolymer (Ireland), crospovidone (Polyplasdone XL) was from ISP Technologies Inc. (USA), partly pregelatinized maize starch (PPS; Starch 1500) was from Colorcon (USA) and sodium starch glycolate (SSG; Primojel) was from DMV International GmbH (The Netherlands).

Alprenolol hydrochloride, amitriptyline hydrochloride, atenolol, cetylpyridinium chloride monohydrate (CPC), diphenhydramine hydrochloride, ethyl hydroxybenzoate (ethylparaben), naproxen sodium salt and sodium salicylate were purchased from Sigma-Aldrich (Sweden) as was the Trizma base for the buffer solutions. Methyl hydroxybenzoate (methylparaben) and propyl hydroxybenzoate (propylparaben) were purchased from Apoteket AB, Production & Laboratories (Sweden). Verapamil hydrochloride was obtained from Knoll AG (Germany). Drug characteristics are presented in Table 1. All chemicals were of analytical grade and used as received. Deionized water was used in all solutions.

Binding study

Substances were dissolved in 5 mM Tris buffer with pH 7.4 ± 0.1, to give a final concentration of 0.2 or 2 mM. The pH was measured after addition of the substance and was readjusted if necessary. The effect of salt was studied by adding NaCl to 5 mM Tris buffer. All use of plastic utensils was avoided to prevent sorption of the amphiphilic substances.

The binding was studied by adding 15 mL drug solution to test tubes containing 50 mg pre-weighed dry disintegrant powder. The samples were rigorously shaken and left for at least 1 h so that the disintegrants formed sediment at the bottom

Table 1 Characteristics of the drug substances used in the experiments

Substance	Charge	pK_a[1]	cLogP[1]
Sodium salicylate	(–)	3.0[2]	2.1[2]
Naproxen	(–)	4.8[2]	3.0[2]
Methyl hydroxybenzoate	(0)	8.3	1.9
Ethyl hydroxybenzoate	(0)	8.3	2.4
Propyl hydroxybenzoate	(0)	8.2	2.9
Atenolol	(+)	9.2	0.097
Alprenolol	(+)	9.2	2.9
Diphenhydramine	(+)	8.8	3.7
Verapamil	(+)	8.8	3.9
Amitriptyline	(+)	9.2	4.9
CPC	(+)	–	5.0

[1]Calculated values (SciFinder 2008); [2]Values for the protonated acid.

of the test tube. If the particles sunk very slowly or not at all, the samples were centrifuged in a Megafuge 1.0 (Heraeus Instruments GmbH, Germany) at 1000 rev min^{-1} for 10 min.

The equilibrium concentration was measured and compared with the drug concentration in the original solution using Unicam UV/vis Spectrometer UV4 (Unicam Atomic Absorption, UK). The absorbance from the disintegrants was generally very low and was also compensated for by subtracting the absorbance from a drug-free experiment. The absorbance was measured at 270 nm for alprenolol, 238 nm for amitriptyline, 274 nm for atenolol, 259 nm for CPC, 258 nm for diphenhydramine, 262 nm for naproxen, 256 nm for the hydroxybenzoates, 296 nm for sodium salicylate and at 278 nm for verapamil.

Drug release measurements

Freshly made, prehydrated SSG gels were used in the drug release experiments. The amount of drug solution necessary to create a fully swollen gel was investigated before the experiments by measuring the amount of liquid absorbed by a known amount of dry SSG through a moist membrane. Gels were thus prepared by adding 11 mL 20 mM diphenhydramine solution or 15 mL 20 mM naproxen solution to 1 g SSG, yielding gels of 8 and 6% SSG, respectively. The resulting drug concentrations in the gels were 17 mM naproxen and 18 mM diphenhydramine. The 5 mM Tris buffer was used as release medium for both naproxen and diphenhydramine. The effect of salt was investigated for diphenhydramine using a release medium of 5 mM Tris buffer supplemented with 145 mM NaCl.

The drug release was measured at room temperature and under sink conditions using custom made diffusion chambers (Björk & Edman 1990). Approximately 1 g gel was weighed onto the donor compartment at the beginning of the experiment. The chamber was then immediately placed on a magnetic stirrer and samples of 1 mL were withdrawn manually from the receiver compartment (16 mL) at 2, 5, 10, 15, 30, 45, 60, 90, 120, 150 and 180 min. Each sample was replaced by 1 mL fresh medium. The drug content was analysed spectrophotometrically.

Calculation of diffusion coefficient

The apparent diffusion coefficients were derived from equation 1, which describes the initial one-dimensional Fickian diffusion from the diffusion chamber under sink conditions:

$$Q = 2C_0(D_{app}t/\pi)^{1/2} \quad (1)$$

In the equation, Q is the amount of drug released per surface area, C_0 is the original concentration of the drug in the gel, D_{app} is the apparent diffusion coefficient of the drug in the gel and t is the time that has elapsed since the initiation of the experiment. The diffusion coefficients were obtained from the gradient of the straight line obtained when the initial drug release (≤ 60% of the total amount) was plotted against the square root of time (Higuchi 1962; Ritger & Peppas 1987).

Statistical analysis

Results are given as mean ± s.d. Statistical differences were evaluated with the statistical software Minitab Release 15 using general linear models followed by Bonferroni's multiple comparison test. A *P*-value of less than 0.05 was regarded as significant.

Results and Discussion

Binding study

The effect of drug characteristics

The substances were chosen according to their physicochemical characteristics to include representatives of positive, negative and neutral drugs. The degree of lipophilicity varied among each substance group to reveal whether the interactions were of electrostatic or lipophilic origin. The results showed that the interactions were most prominent between the cationic substances and the two superdisintegrants SSG and CCS that formed anionic gels upon hydration (Figure 1). The weakly basic drugs atenolol, alprenolol, diphenhydramine and verapamil were all absorbed to approximately the same amount: approximately 30% for SSG and 60% for CCS, which contained more anionic groups (Table 2). The

Table 2 The percentage of the original concentration (0.2 or 2 mM) remaining in solution after the addition of 50 mg disintegrant

Disintegrant	SSG (%)		CCS (%)		PPS (%)		Crospovidone (%)	
[Original concn] Substance[1]	[0.2 mM]	[2 mM]	[0.2 mM]	[2 mM]	[0.2 mM]	[2 mM]	[0.2 mM]	[2 mM]
(−) Sodium salicylate	103.4 ± 0.5	103.0 ± 2.9	104.6 ± 1.8	99.8 ± 1.0	98.8 ± 0.7	96.1 ± 2.2	98.4 ± 0.8	97.7 ± 1.0
(−) Naproxen	100.8 ± 1.5	102.9 ± 1.1	103.7 ± 0.8	102.5 ± 0.4	99.2 ± 1.0	97.6 ± 1.0	96.1 ± 1.1	97.5 ± 0.9
(0) Methyl hydroxybenzoate	103.4 ± 0.5	103.0 ± 2.9	98.6 ± 1.2	96.7 ± 0.7	97.1 ± 1.9	97.3 ± 1.1	87.5 ± 1.6	88.7 ± 0.2
(0) Ethyl hydroxybenzoate	91.7 ± 3.2	95.3 ± 1.4	97.2 ± 1.3	95.8 ± 1.0	95.2 ± 1.1	98.0 ± 2.1	88.6 ± 2.1	87.8 ± 3.4
(0) Propyl hydroxybenzoate	94.3 ± 3.5	94.7 ± 0.4	98.8 ± 0.9	92.1 ± 0.5	92.6 ± 1.0	92.5 ± 1.2	84.3 ± 0.6	75.9 ± 0.4
(+) Atenolol	69.5 ± 0.7	63.7 ± 0.9	38.6 ± 1.6	48.0 ± 1.2	87.7 ± 1.2	97.9 ± 0.3	96.5 ± 3.0	99.0 ± 1.0
(+) Alprenolol	69.2 ± 0.9	74.4 ± 1.1	36.8 ± 2.7	48.8 ± 0.3	89.5 ± 2.7	96.4 ± 0.9	96.6 ± 0.3	98.3 ± 0.4
(+) Diphenhydramine	61.0 ± 0.7	67.2 ± 0.4	59.0 ± 3.6	42.8 ± 1.3	83.9 ± 3.0	93.9 ± 1.3	98.4 ± 5.9	98.8 ± 0.3
(+) Verapamil	69.7 ± 0.3	70.4 ± 1.7	45.3 ± 1.4	23.5 ± 0.3	90.3 ± 11.8	97.0 ± 2.4	97.6 ± 0.9	99.0 ± 2.4
(+) Amitriptyline	46.0 ± 0.4	40.9 ± 2.0	25.7 ± 0.5	10.7 ± 0.5	89.7 ± 0.8	92.2 ± 2.0	95.5 ± 0.7	96.4 ± 4.7
(+) CPC	4.7 ± 0.7	1.7 ± 0.1	4.8 ± 1.1[2]	30.3 ± 2.1[2]	44.1 ± 4.7	8.8 ± 0.2	98.7 ± 0.3	100.2 ± 1.0

Mean values ± s.d., n = 3. [1]Net charge indicated within parentheses; [2]The values were most likely overestimated because of an opaque supernatant.

fact that the most hydrophilic compound, atenolol, was absorbed to the same degree as the three more amphiphilic substances suggested that the mechanism behind the absorption was purely ion exchange. Amitriptyline has a more pronounced amphiphilic character (Table 1) and was also absorbed to a significantly higher extent, which suggested that the ion exchange was amplified by some degree of aggregation within the gels. The most distinct interaction was observed with the cationic surfactant CPC, which was almost completely absorbed by the anionic polymers. This indicated that the concentration of the surfactant was above its CAC and that extensive aggregate formation took place within the gels. CPC formed a complex with CCS, which produced an opaque liquid that was not possible to separate and also increased the measured absorbance in the UV-absorbance measurements. The concentration of CPC still in solution was therefore almost certainly lower than what has been indicated in Table 2.

No substantial evidence of purely lipophilic interactions could be detected between the hydroxybenzoates and the two anionic superdisintegrants or with their unsubstituted comparator. An interesting observation was that the unsubstituted and non-ionic PPS interacted with CPC although no interactions were seen between this disintegrant and the other cationic substances. The absorption could either have been caused by lipophilic or electrostatic interactions. However, if lipophilic interactions had been the main cause, binding should likely have been observed to the non-ionic superdisintegrant crospovidone. It therefore seemed that the unsubstituted starch contained a small amount of charged elements.

As expected the hydrophilic, but non-ionic, superdisintegrant crospovidone did not show any tendency towards electrostatic interactions. Yet the hydroxybenzoates were absorbed to a higher degree by this superdisintegrant, which suggested a significant effect of lipophilic interactions. The most pronounced effect was seen with the most lipophilic substance, propyl hydroxybenzoate, where as much as 24% was absorbed from the 2 mM solution.

The binding was evaluated at two pharmaceutically relevant drug concentrations (0.2 and 2 mM) to investigate if the binding was proportional to the concentration. A much higher binding at the higher concentration could indicate that the CAC was reached within this concentration range. The binding of CPC to PPS was indeed higher at 2 mM (9% remained in solution compared with 44% at 0.2 mM), which could be deduced to the CMC value of CPC that should be just below 1 mM (Garcia-Mateos et al 1997), given that there were some anionic groups within the PPS as discussed above. Also diphenhydramine, verapamil and amitriptyline seemed to bind to CCS to a higher degree at the higher concentration (42, 24 and 11% remained in solution compared with 59, 45 and 26% at 0.2 mM, see Table 2). The CMC values for diphenhydramine and amitriptyline have been reported to be 105 and 25 mM, respectively, in 150 mM NaCl (Bramer et al 2003), whereas the CMC value of verapamil has been suggested to be as low as 13 mM, where dimers were formed in pure water (Taboada et al 2001). The enhanced absorption was, however, not comparable with the clearly cooperative binding of CPC and it therefore seemed unlikely that the concentration of 2 mM was above the CAC for the drug substances. Even so, the higher substance concentration was chosen for the evaluation at physiological salt concentrations as substantial interactions at this concentration would indicate that they were driven by more than ion exchange.

The effect of salt

Lipophilic interactions are likely to increase with an increased salt concentration, whereas ion exchange interactions will decrease because of a smaller relative gain in entropy from the release of counter-ions. The physiological salt concentrations successfully extinguished the interactions with the weakly basic drugs (Figure 2), which corroborated the previous assumption that these were caused by ion exchange. For example, the binding of the amphiphilic diphenhydramine was decreased by 86 and 97% to 24.4 and 11.4 μmol g^{-1} for SSG and CCS, respectively, when expressed as the drug amount bound per dry weight of the disintegrant powder. Amitriptyline had a more pronounced amphiphilic character, yet the binding to CCS was still decreased by 96% to 20.9 μmol g^{-1}. SSG contained a lower degree of charged groups than CCS and a significantly higher binding of amitriptyline (88.2 μmol g^{-1}) was seen at the higher salt concentration, which may have been attributed to some degree of lipophilic interaction causing an increased aggregation tendency. However, it cannot be compared with the binding of CPC that only decreased by 14% after the addition of salt and still was as high as 529 μmol g^{-1}. In this case it was obvious that a stronger interaction was achieved, likely by aggregation of the surfactant inside the polymer. The quantitative measure of the interaction between CCS and CPC was still complicated by their strong interaction that made a clear supernatant unattainable; the binding of CPC was consequently, in all probability, higher than what has been indicated in Figure 2.

The nearly complete suppression of the interaction between PPS and CPC from 559 to 86.0 μmol g^{-1} after the addition of salt strengthened the theory that there were some charged elements within the PPS structure, but indicated that no extensive aggregate formation took place within the disintegrant. The lipophilic interactions seen between crospovidone and propyl hydroxybenzoate were still present at the higher salt concentration although with a significantly lower value (117 μmol g^{-1}) compared with the original (144 μmol g^{-1}). The same trend seemed to be followed by the other disintegrants, although an increased lipophilic interaction would have been expected at higher salt concentrations. Nevertheless, the lipophilic interaction with crospovidone was comparable with the electrostatic interaction seen between the amphiphilic amitriptyline and SSG at physiological salt concentrations. The in-vivo impact of these interactions would depend on the proportion of drug and disintegrant and was therefore difficult to predict. A binding of 100 μmol g^{-1} would approximately correspond to ≤ 1 μg of a substance (molecular weight ≤ 500 g mol^{-1}) being bound to 20 mg disintegrant. Unless the drug dose was very low or the amount of disintegrant was very high, it does seem unlikely that the interactions would affect the bioavailability in-vivo. Positive results from a clinical study with a nasal powder formulation consisting of SSG and a low dose

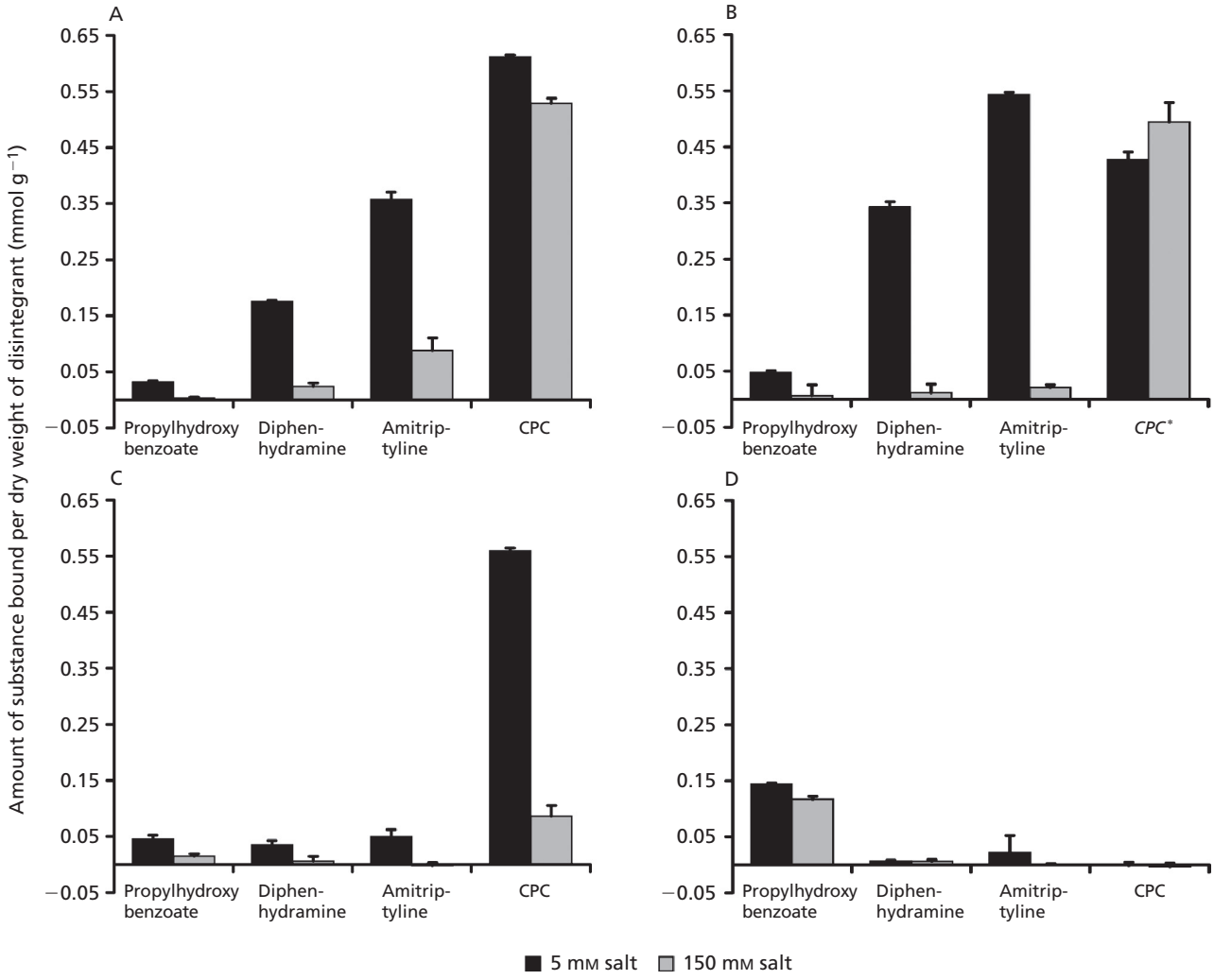

Figure 2 The effect of salt on the interaction of 2 mM propyl hydroxybenzoate (propylparaben), diphenhydramine, amitriptyline and CPC with (A) SSG, (B) CCS, (C) PPS and (D) crospovidone. The interaction is described as the drug amount (mmol) bound per dry weight of the disintegrant (g). Mean values ± s.d., n = 3. *The values for the binding of CPC to CCS were most likely underestimated because of an opaque supernatant.

cationic substance have been obtained by our research group (unpublished data). This was a further indication that the ion exchange effect should be of low impact in-vivo.

The effect of salt was more thoroughly investigated for SSG and exemplified by its interaction with diphenhydramine. As can be seen in Figure 3, the binding was highly dependent on the salt concentration in the liquid and the exponential decrease showed that even a small change in ionic strength could have a pronounced effect on the amount absorbed. Depending on the amount of superdisintegrant and the liquid volume used, this may lead to significant variations in the results of in-vitro experiments. The amount of salt in the disintegrant could even be of significant importance for the resulting salt concentration in the solution if pure water is used; SSG can contain up to 7% NaCl (Rowe et al 2005), which may cause variations from batch to batch or depending on which brand is used (Edge et al 2002); in-vitro comparisons and in-vivo correlations are thus impeded unless a salt solution is used.

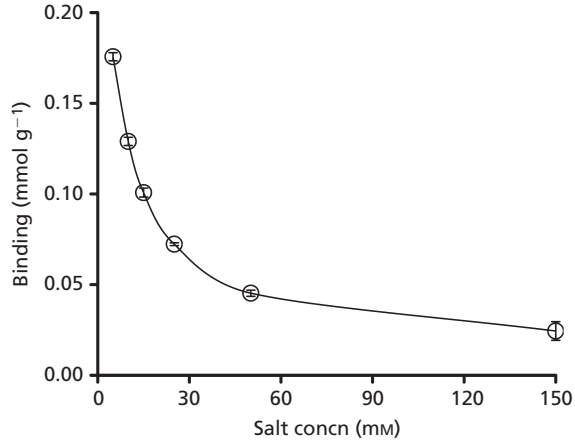

Figure 3 The effect of increased ionic strength on the binding of diphenhydramine from a 2 mM solution to SSG expressed as mmol diphenhydramine per dry weight of SSG (g). Mean values ± s.d., n = 3.

Drug release measurements

The effect of the interactions on drug release was exemplified by the release from prehydrated SSG gels (Figure 4). The release of the anionic naproxen to 5 mM Tris buffer was very fast and the equilibrium concentration (100% released) was obtained within 2 h. The corresponding release of diphenhydramine was substantially delayed and did not reach more than 43% released within 3 h, which was most likely caused by electrostatic interactions between drug and polymer. When the ionic strength in the release medium was increased to 150 mM, the release was also higher and reached 82% after 3 h. The corresponding apparent diffusion coefficients were $11.5 \pm 1.6 \times 10^{-6}$ and $1.52 \pm 0.1 \times 10^{-6}$ $cm^2\ s^{-1}$ for naproxen and diphenhydramine, respectively, to 5 mM Tris buffer. The higher salt concentration of 150 mM gave a significant increase in the apparent diffusion coefficient of diphenhydramine to $5.2 \pm 1.2 \times 10^{-6}$ $cm^2\ s^{-1}$. The latter value is well in accordance with a reported value of $6.5 \pm 0.3 \times 10^{-6}$ $cm^2\ s^{-1}$ for the release of 18 mM diphenhydramine from hydrophilic carbomer (carbopol) at 150 mM NaCl (Paulsson & Edsman 2002), despite the higher polymer concentration used herein (8% compared with 1% carbomer). In this context it was also worth noticing that the gel prepared in the diphenhydramine solution contained more SSG (8%) than the gel prepared in naproxen solution (6%). The fact that SSG did not manage to absorb as much fluid in the presence of diphenhydramine implied that an interaction took place, which shielded the repulsive forces between the polymer chains and caused the gel to shrink.

The fractions released at the different salt concentrations were in agreement with the interaction observed in the binding study; 43% released indicated a binding of 120 μmol g^{-1} and 82% corresponded to 40 μmol g^{-1}, which could be compared with the 176 and 24.4 μmol g^{-1}, respectively, reported above. The interactive system for nasal administration described by Fransén et al (2007) was not likely to contain more than 5% (w/w) of the active component. If we compared this with the binding of diphenhydramine it would mean that in-vitro experiments in pure water should give approximately 20% released, whereas 90% would be released at a physiological salt concentration, exemplifying the importance of the ionic strength used in-vitro. A direct in-vivo correlation of the release rate would be difficult to make as the substance could be dissolved and absorbed into the blood stream before the mucoadhesive particle was fully hydrated when administered as an interactive mixture. The gel particles would also spread over a larger surface area which would decrease further the drug release time. The in-vitro experiments on prehydrated gels at an isotonic salt concentration could therefore be used as a worst-case scenario for the in-vivo absorption.

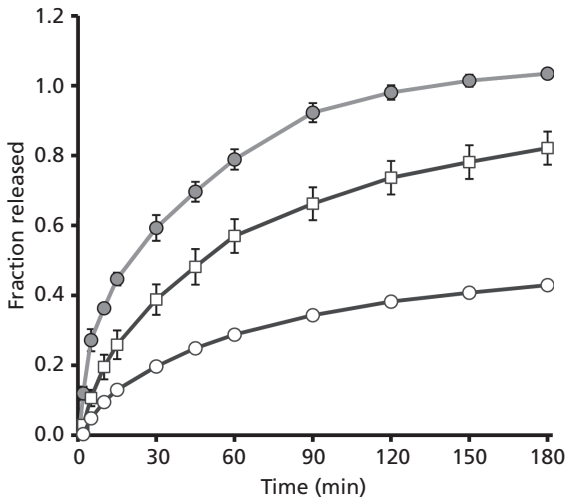

Figure 4 The cumulative release of naproxen (●) or diphenhydramine (○□) to 5 mM Tris buffer (●○) or 5 mM Tris buffer supplemented with 145 mM NaCl (□) from SSG gels. Mean values ± s.d., n = 3.

Conclusion

Cationic substances are susceptible to absorption through ion exchange when exposed to anionic superdisintegrants (SSG and CCS). A pronounced amphiphilic structure will give rise to stronger interactions, possibly by the formation of aggregates inside the gel. The anionic polymers did not interact with either the anionic or non-ionic drugs, whereas the non-ionic superdisintegrant crospovidone only interacted with the lipophilic hydroxybenzoates. At physiological salt concentrations the lipophilic interactions remained, whereas the ion exchange interactions with the weakly basic drugs were clearly reduced. Strong binding caused by aggregation within the gel was obtained between CPC and the two anionic gels and could not be diminished by an increased salt concentration. However, the drug substances studied did not seem to be surface active or flexible enough to induce such interactions. The effect of an increased salt concentration was most pronounced at lower ionic strength and in-vitro studies should therefore preferably be performed at physiological salt concentrations to avoid unnecessary variations. The release profile of diphenhydramine was significantly affected by the addition of salt in the release medium and physiological salt concentrations should be chosen to give an indication of the in-vivo release. The ion exchange interactions could cause a slight delay in the in-vivo release, but would be unlikely to influence the final bioavailability.

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