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Research Article

Impact of Physicochemical Environment on the Super Disintegrant Functionality of Cross-Linked Carboxymethyl Sodium Starch: Insight on Formulation Precautions

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Abstract. The aim of this work is to improve the understanding of the physicochemical mechanisms involved in the functionality of cross-linked carboxymethyl sodium starch (CCSS) as a tablet super disintegrant (SD). The behavior and properties of this SD (medium uptake, disintegration times, particle size, and rheology) was investigated in a wetting medium of different physicochemical properties. In particular, the relative permittivity (dielectric constant) of these media was intentionally modified for evaluating its effect on CCSS properties. Results showed different swelling behaviors of CCSS particles according to the relative permittivity of the tested media and allow to propose two underlying mechanisms that explain CCSS functionality. Both the intra-particular swelling and the inter-particular repulsion are affected by the relative permittivity of the media. Finally, disintegration test performed on tablets specially formulated with mannitol (used commonly as an excipient and known to modify relative permittivity) confirmed that the functionality of CCSS and therefore the disintegration of the tablet can be altered according to the mannitol content.

KEY WORDS: cross-linked carboxymethyl sodium starch; disintegrant functionality; orally disintegrating tablets; relative permittivity; repulsive layers.

INTRODUCTION

Tablets are solid oral dosage forms obtained by compression and deformation of solid particles. The forces during the compression cycle contribute to maintaining the particles of excipients and active pharmaceutical ingredients (API) together through different cohesive forces. In order to overcome these cohesive forces and ensure tablet disintegration followed by API dissolution after ingestion, tablets must contain disintegrants in their formulation. For rapidly disintegrating tablets (soluble, dispersible, and orally disintegrating tablets), the disintegration must be very fast and initiated with a little quantity of a wetting medium. Excipient manufacturers have come up with a class of excipients such as cross-linked carboxymethyl sodium cellulose (croscarmellose), cross-linked carboxymethyl sodium starch (CCSS), and cross-linked poly(vinyl pyrolidone) (crospovidone) called super disintegrants" (SD) in order to overcome this challenge (1). These excipients are able to overcome the cohesive forces binding the different particles between each other in a very short period of time and with very little wetting medium. SD are used because they are more effective at lower concentrations with greater disintegrating efficiency and mechanical strength than their traditional counterparts. Their likely mechanisms of action is a combination of proposed theories including water wicking, swelling, deformation recovery, repulsion, and heat of wetting (2,3). However, formulations with SD remain complex (4). Disintegration kinetics as well as the shape and size of the resulting particles are not always constant. Literature has reported a strong influence of different parameters on the disintegration efficacy. These parameters can be classified in four different categories related to (i) the SD itself, (ii) the formulation components, (iii) the compaction process, and (iv) the physicochemical environment of the SD during the disintegration. SD parameters such as distribution and concentration in the tablet (5), particle granulometry, mixed powders' bulk density, compression mode, and the resulting tablet porosity are all parameters which have shown to influence the disintegration efficacy (6–9), as well as the solubility, the hydrophilic nature of the formulation components, and the pH of the disintegrating medium (7,10,11). Even if these previous studies show an influence of the formulation on the disintegration processes, there is still lacking explanation on the physicochemical phenomena that explain the

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influence of the formulation on the disintegration processes.

Therefore, the novelty of this work is to gain insight on the physicochemical phenomena which contribute to this formulation-dependent behavior of a charged SD: cross-linked carboxymethyl sodium starch (CCSS) (Fig. 1). CCSS is produced by the cross-linking of native starch followed by carboxymethylation. The optimum balance between the molecular weight, the degree of substitution, and the extent of cross-linking allows for rapid water uptake by the polymer without the formation of a viscous gel that might impede dissolution (12). Its primary mechanism of disintegration capacity is thought to be due to its important swelling capacity upon wetting (10,13). When a tablet is immersed in a wetting medium, depending on the solubility of the formulation components, they can dissolve in the uptaken medium. The dissolution of these components can change the physicochemical nature of the uptaken medium, giving rise to a new chemical environment in the pore network of the tablet. This effect is even more important when using SD that is triggered by a very little volume of wetting medium.

In this work, our strategy consisted in evaluating the influence of the modifications of the physicochemical environment of the SD that can result from the dissolution of formulation components in the pore network of a tablet. More specifically, we simulated excipient dissolution which can change the relative permittivity of a medium in which they dissolve and influence the disintegrating capacities of CCSS.

In a first part of this study, we evaluated the macroscopic changes such as wetting medium uptake, wet CCSS particle size, and tablet disintegration times in media of different relative permittivity. We then evaluated the viscosity of diluted suspensions of CCSS in these media for the calculation of the rheological solid volume fraction. Finally, we formulated tablets with different mannitol concentrations and evaluated their disintegration time. The choice of this excipient is in relation to its extensive use in formulation for direct compression and orally disintegrating tablets (8,14) as well as its ability to change the relative permittivity of aqueous medium in which it is dissolved (15,16).

MATERIALS AND METHODS

Materials

CCSS (Glycolys® Standard Grade) and mannitol (Pearlitol SD®) was generously sampled by Roquette SA, Lestrem, France. Calcium hydrogen phosphate dihydrate (CHP) (Emcompress®) was obtained from JRS Pharma, St-Germain en Laye, France, and was chosen because it is an inert excipient regarding disintegration. Magnesium stearate (MgSt) was obtained from Cooper, Lyon, France. The solvents were distilled water and absolute ethanol from Sigma, Saint-Quentin Fallavier, France.

Methods

In order to simulate media of different relative permittivity (ε_r), specific solutions were prepared by mixing ethanol and water in different proportions (17) as well as using saturated mannitol solutions (16) (Table I). Tablets of a 600-mg weight (60–80 N) were produced by direct compression on a Frogerais OA press, equipped with a 12-mm flat punch. Two different qualitative formulations were used (Table II). The formulations without mannitol were used for the disintegration test in wetting media of different relative permittivity. The formulations with different quantities of mannitol were used for the disintegration test in distilled water.

Disintegration Test

Disintegration time was done on a normalized European Pharmacopeia apparatus at 25°C in the different tested media (Table I). Complete disintegration time was recorded when there were no more particles on the sieve at the bottom of the basket. The results are presented as a mean of six tablets in each medium with the corresponding standard deviation.

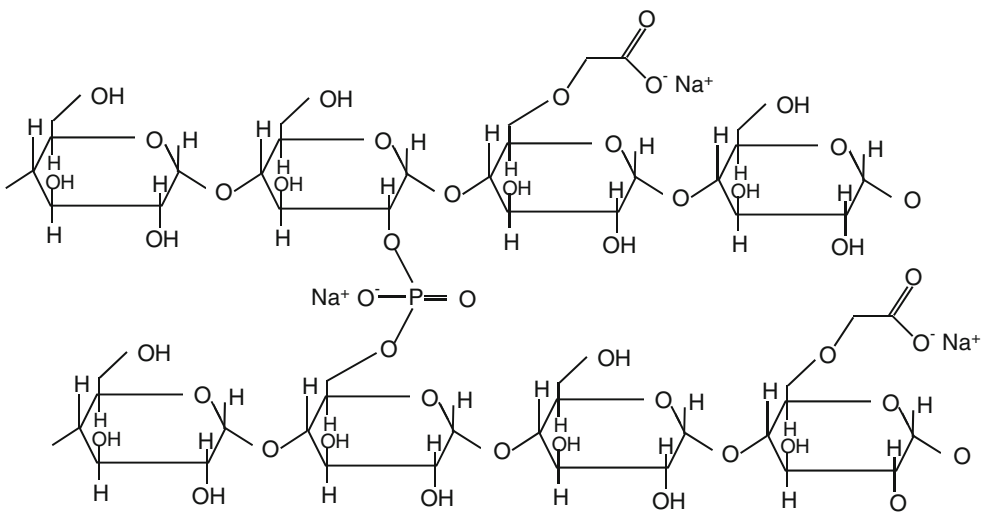

Fig. 1. Chemical structure of CCCS

Table I. Compositions and Relative Permittivity Constants (ε_r) of Different Wetting Media

	Ethanol				Mannitol
Weight percent in water (%wt)	0	10	25	50	21
ε_r (/)	80.4	74.8	66.4	52.4	75.6

Wetting Medium Uptake

Wetting medium uptake was evaluated by placing 300 mg of CCSS powder in a glass test tube. Increasing quantities of the different wetting media were added stepwise (0.1 mL) to the tubes. Maximum wetting medium uptake was determined when the swollen CCSS particles were able to flow freely upon tube inversion.

Particle Size Determination

Particle sizes of CCSS in different wetting media were measured by a laser diffraction technique using a particle analyzer (Mastersizer 2000, Malvern Instruments) with a dispersing wet module. Two sets of light sources (helium-neon and argon) gave a measuring size range of 0.02–600 μm. Fifty milligrams of dry CCSS powder was dispersed in 50 mL of the specific studied medium. The suspension was stirred for 15 min. This time was determined experimentally to give stable particle sizes, and swelling was thus considered to be at equilibrium. Adequate dispersion into primary particles was checked by light-transmission microscopy (Axioplan, Carl Zeiss Microscopy, Jena, Germany). The suspension was added to a stirred sample cell containing the specific studied medium to obtain an obscuration value of 15%. A cycle of five measurements over 4 s was initiated after 1 min of circulation. The analysis was repeated once with a new sample from the same initial suspension. The sample unit was rinsed twice with the studied wetting medium between measurements. The size distribution was calculated by Mie theory using the refractive indices of starch 1.335 and water or ethanol/water mixes between 1.330 and 1.345, respectively (18).

Rheology

Rheological experiments were performed on a rotational rheometer (Anton Paar, Physica MCR 301). A coaxial cylindrical measurement device with a double gap measuring system was used. The temperature was maintained constant at 20 ±0.1°C. The volume of sample used for each measurement was 7 mL. An increasing ramp of shear rate from 1 to 200 s^{-1} was applied to the diluted suspensions of CCSS. Two different concentrations of CCSS, 1 and 2 $g.L^{-1}$, were tested in each wetting medium. Viscosity was measured at a shear rate of 53 s^{-1} which is located in the field of Newtonian behavior for the suspensions as well as the different pure suspending media (Fig. 2).

Table II. Tablet Formulations Used for the Disintegration Test in Wetting Media of Different Relative Permittivity

Formulation mg (%)			
CCSS	MgSt	Mannitol	CHP
18 (3)	3 (0.5)	0 (0)	579 (96.5)
18 (3)	3 (0.5)	60 (10)	519 (86.5)
18 (3)	3 (0.5)	180 (30)	399 (66.5)
18 (3)	3 (0.5)	360 (60)	219 (36.5)
18 (3)	3 (0.5)	540 (90)	39 (6.5)

CCSS cross-linked carboxymethyl sodium starch, *MgSt* magnesium stearate, *CHP* calcium hydrogen phosphate dihydrate

RESULTS AND DISCUSSION

Disintegration Test

Figure 3 shows an exponential relation between relative permittivity and disintegration time suggesting an underlying dependency between CCSS functionality and relative permittivity. In pure water, the disintegration time of CCSS tablets is relatively fast and becomes slower as the ethanol content increases in the disintegration medium. The first three highest relative permittivity wetting media have a near-linear relation with the disintegration time; however, when testing water/ethanol 50/50, the disintegration becomes excessively long. The disintegration time in saturated mannitol solutions was also determined and fell within the values of the corresponding calculated relative permittivity.

Wetting Medium Uptake

Figure 4 shows that the wetting medium uptake by the CCSS particles increases linearly with the relative permittivity. Medium uptake can be translated in the solvating capacity of the CCSS particles by the medium. As the relative permittivity of the medium decreases, it is less capable of solvating the CCSS particles and interacts to a lesser extent with the CCSS particles. The medium is therefore more readily available to contribute as a simple suspending medium allowing the free-flowing of the particles upon tube inversion. These results suggest that the relative permittivity of the wetting medium can influence the SD functionality and thus the tablet disintegration time by modifying the SD's capacity of uptaking the wetting medium or more precisely of the solvating capacity of the wetting medium.

Particle Size Determination

Figure 5 shows that the volume-mean particle diameter (d_{50}) increases linearly as the relative permittivity increases. Since the SD particles are composed of cross-linked polymeric chains, the particles cannot completely dissolve and give rise to a swollen particle upon chain solvation. These results confirm that the liquid's relative permittivity influences the capacity of the SD particle to swell. More precisely, the swelling is due to the intra-particular polymer chain interactions which thus vary according to the relative permittivity of the solvating medium as explained further on. Size determination in a saturated mannitol solution gave a result that was slightly lower than expected by the ethanol/water mixes, but still very close to the expected size. The small difference can be due to the

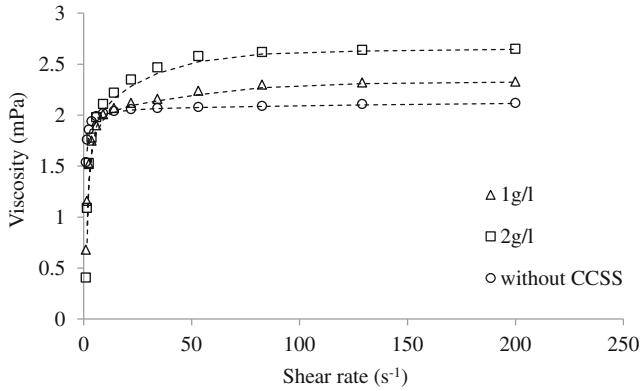

Fig. 2. Flow curves for various CCSS concentrations (0, 1, and 2 g.L^{-1}) in 75/25 water/ethanol

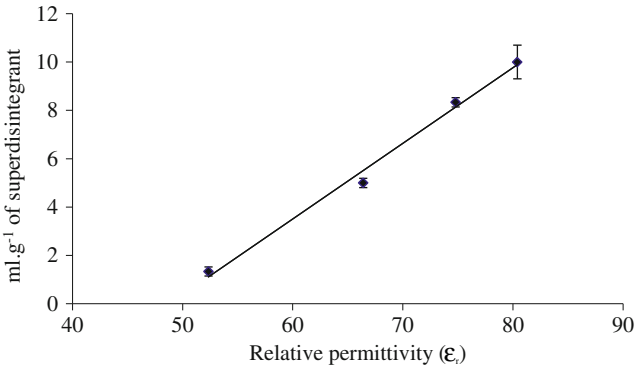

Fig. 4. Liquid uptake as a function of relative permittivity

different refractive indexes of water/ethanol mixes compared to saturated mannitol solutions.

Rheology

Rheology studies were done with the intention of showing a supplementary phenomenon that can explain the different functionality of the SD particles. Other than swelling due to intra-particle interactions, an electrical double layer, known as the Stern and diffuse layers, is also affected by the wetting medium's relative permittivity.

The viscosity of a suspension (μ) is greater than that of the pure suspending medium (μ_0), owing to the perturbation of the shear field in the vicinity of the particles. At low concentrations, the Stokes-Einstein equation (19,20) (Eq.1) allows calculating a solid volume fraction (ϕ) of uncharged solid spherical particles (21):

$$(\mu-\mu_0)/\mu_0 = 2.5\ \phi \quad (1)$$

where $(\mu-\mu_0)/\mu_0$ is the specific viscosity. However, when the particles are charged such as CCSS particles, the flow in the vicinity of the particles is modified due to the presence of counter-ions within the electrical double layer (22). This effect is known as the electroviscous effect calculated according to Eq. 2:

$$(\mu-\mu_0)/\mu_0 = 2.5\ \phi(1+p) \quad (2)$$

where p is the primary electroviscous coefficient and is a function of particle charge and the ions present in the medium. The primary electroviscous effect describes the hydrodynamic radius of the particles and indirectly the dynamic Stern layer (immobilized hydrated counter-ions cloud surrounding each particle) (22). In order to account for the electroviscous effect, we tested the evolution of the specific viscosity as a function of the concentration of the CCSS particles in the different tested media. Figure 6 shows a linear relation between the specific viscosity and the concentration in every medium. Moreover, Fig. 7 shows that the slope S of this linear function increases according to the relative permittivity of the medium. These slopes thus translate the behavior resulting from two phenomena explaining the functionality of the CCSS particles. First of all, they translate the swelling of the particle due to the solvation effect of the polymeric chains through the solid volume fraction (ϕ) as seen previously. More interestingly, the electroviscous effect also translates the hydrated charged Stern layer surrounding the particle. Rheology experiments therefore allow appreciating the change in dimensions of the CCSS particles due to the intra-particle swelling as well as the change in the hydrated Stern layer surrounding the particles.

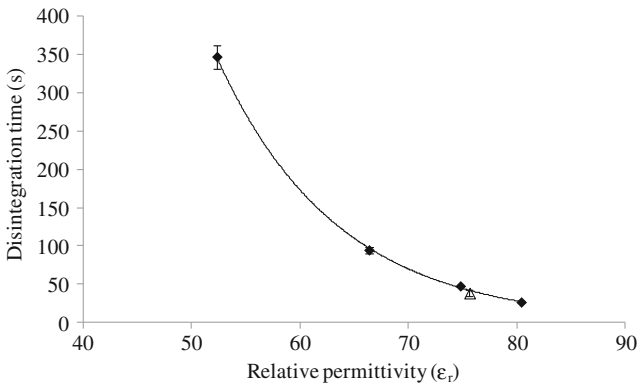

Fig. 3. Tablet disintegration as a function of relative permittivity (*filled diamonds* represent ethanol/water solutions and *empty triangle* indicates saturated mannitol solution)

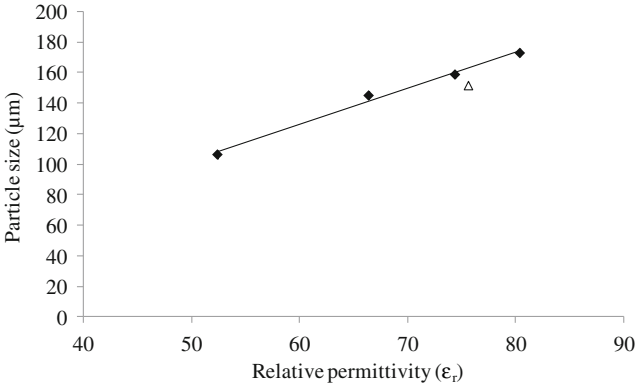

Fig. 5. Particle size as a function of relative permittivity (*filled diamonds* represent ethanol/water solutions and *empty triangle* indicates saturated mannitol solution)

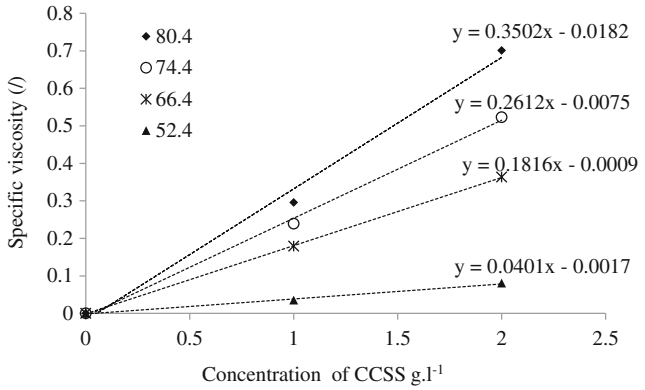

Fig. 6. Specific viscosity *versus* concentration for the dispersion of CCSS in various liquids

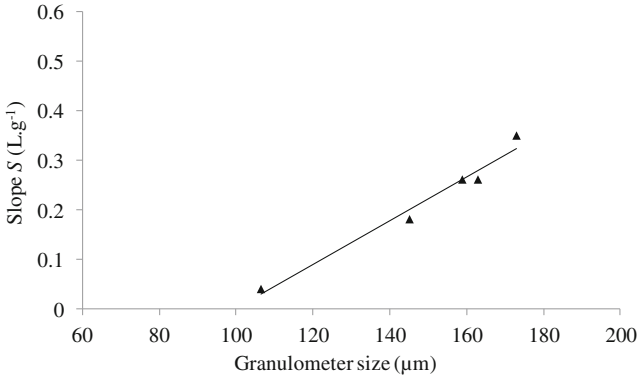

Fig. 8. Slope *S* as a function of relative permittivity

Furthermore, when comparing the evolution of the slope *S* to sizes observed through laser granulometry in Fig. 8, it is possible to confirm that both phenomena evolve similarly in the different media.

The use of the DLVO theory has been recently used as a simulation tool to explain disintegration mechanism on a fundamental level (23). Our experimental results confirm the implication of the DLVO theory for the charged SD. The physicochemical explanation of the two phenomena involved relies in the capacity of the medium to ionize and dissociate the carboxylate functions of the CCSS. In a high relative permittivity environment such as water, one can expect a higher dissociation and ionization of the carboxylate functions. The resulting repulsion between the ionized functions thus creates swelling since the chains cannot completely dissolve due to cross-linking. Equally in these conditions, the particle becomes very electronegative with an increase of the surface charges. The negativity of the particle attracts counterions (Na^+ dissociated) to form a firmly attached Stern layer around the surface of the particle. This layer can be associated with a diffuse layer in which the ions' concentration gradually decreases with distance from the Stern layer until it reaches equilibrium with the ion concentration in the suspending medium (this diffuse layer cannot exist in our experiments, because co-ions are not present in the medium). The extended DLVO (Derjaguin, Landau, Verwey, and Overbeek) theory which adds hydration forces to the repulsive forces between two particles explains how two particles can interact with each other according to the balance in the attractive Van der Walls forces and the repulsive (electrostatic and hydration) forces (24–26). In the completely dissociated state, electronegative CCSS are surrounded by a dense cationic layer, and the repulsive inter-particular forces are more important. As the relative permittivity decreases, dissociation and the repulsive inter-particular become less important explaining the drop of the specific viscosity with the increase of ethanol ratio.

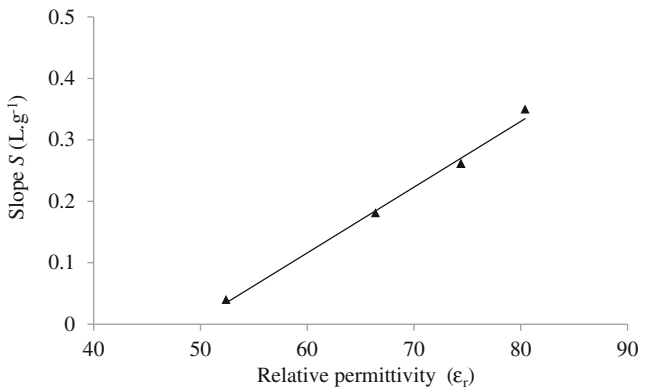

Fig. 7. Slopes *S* *versus* relative permittivity for the dispersion of CCSS in various liquids

Formulated Tablet Disintegration

Mannitol is extensively used as an excipient in tablet formulation. It is known for influencing the relative permittivity of an aqueous medium after its dissolution (16). Therefore, we studied the disintegration time of formulated tablets with CCSS and mannitol in water. Figure 9 shows that despite the highly hydrophilic and soluble mannitol, disintegration time increases as mannitol concentration increases in the tablet.

The tablet uptakes water through its porous network, mannitol dissolves in the water and thus changes the relative permittivity of the wetting medium. Intra-particle swelling of the CCSS decreases as does the inter-particular electrostatic and hydratation repulsions resulting in a less functional SD and a slower disintegrating tablet. Above 30% of mannitol in the tablet, the inhibitory effect on the functionality of the SD is not as important as at the lower mannitol concentrations. This is explained by the fact that mannitol is very soluble; and at a higher mannitol concentration, the dissolution of the mannitol itself leaving increasingly void spaces in the tablet

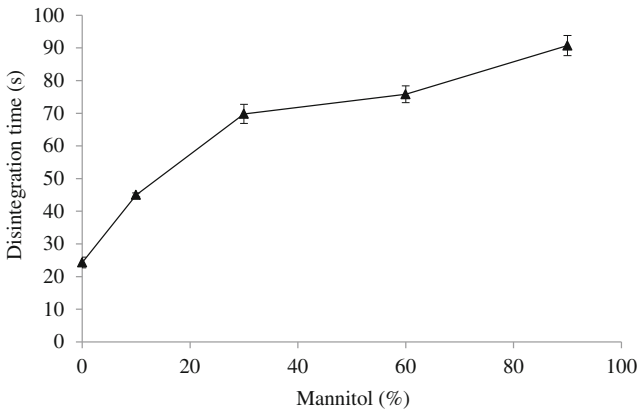

Fig. 9. Disintegration time (s) *versus* mannitol concentration in tablets

compensates for its inhibiting effect of the CCSS disintegrating functionality.

CONCLUSION

Although the experimental conditions in this study do not completely reflect pharmaceutical tablet *in vivo* dispositions, the results showed an important influence of the relative permittivity on the CCSS functionality. CCSS is an ionic super disintegrant, and its functionality is dependent on the dissociation of the carboxylate functions. By varying the relative permittivity, we influenced the dissociating capacity of the different media. This dissociating capacity has repercussions on the swelling capacity of the CCSS particle as well as on the repulsive forces surrounding the particle. We also showed that a very common excipient used in tablet formulation can have an effect on the CCSS functionality. The comprehension of this behavior is very important when elaborating tablet formulations. Very common excipients (mannitol, polyethylene glycol, *etc.*) can influence the relative permittivity of the wetting medium. Furthermore, these results lead the way to following studies that will show the effect on other formulating elements (excipients or active ingredients) such as ionic, acidic, or basic compounds that can directly influence the dissociating capacity of the super disintegrant and its functionality.

REFERENCES

1. Kraemer J, Gajendran J, Guillot A, Schichtel J, Tuereli A. Dissolution testing of orally disintegrating tablets. J Pharm Pharmacol. 2012;64:911–8.
2. Hersen-Delesalle C, Leclerc B, Couarraze G, Busignies V, Tchoreloff P. The effects of relative humidity and superdisintegrant concentrations on the mechanical properties of pharmaceutical compacts. Drug Dev Ind Pharm. 2007;33:1297–307.
3. Christian MR. Disintegrants in tabletting. In: Augsburger LL, Hoag SW, editors. Pharmaceutical dosage form: tablets. New York: Informa; 2008. p. 219–22.
4. Claudius JS, Neau SH. Kinetic and equilibrium characterization of interactions between glycopeptide and sodium carboxymethyl starch. Int J Pharm. 1996;144:71–9.
5. Luginbühl R, Leuenberger H. Use of percolation theory to interpret water uptake, disintegration time and intrinsic dissolution rate of tablets consisting of binary mixtures. Pharma Acta Helv. 1994;69:127–34.
6. Lahdenpää E, Niskanen M, Yliruusi J. Crushing strength, disintegration time and weight variation of tablets compressed from three Avicel PH grades and their mixtures. Eur J Pharm Biopharm. 1997;43:315–22.
7. Bele MH, Derle DV. Mechanism of disintegration of polacrilin potassium: swelling or wicking? Acta Pharm Sin B. 2012;21:70–6.
8. Yamamoto Y, Fujii M, Watanabe KI, Tsukamoto M. Effect of powder characteristics on oral tablet disintegration. Int J Pharm. 2009;365:116–20.
9. Vromans H, Bolhuis GK, Lerk CF, Kussendrager KD. Studies on tableting properties of lactose VIII. The effect of variations in primary particle size, percentage of amorphous lactose and addition of a disintegrant on the disintegration of spray-dried lactose tablets. Int J Pharm. 1987;39:201–6.
10. Caramella C, Colombo P, Conte U, Ferrari F, Gazzaniga A, LaManna A, *et al.* A physical analysis of the phenomenon of tablet disintegration. Int J Pharm. 1988;44:177–86.
11. Zhao N, Augsburger LL. The influence of swelling capacity of superdisintegrants in different pH medium on the dissolution of hydrochlorothiazide from directly compressed tablets. AAPS PharmSciTech. 2005;6:120–6.
12. Seidel C, Kulicke WM, Heß B, Hartmann C, Dieter Lechnerb M, Lazik W. Synthesis and characterization of cross-linked carboxymethyl potato starch ether gels. Starch-Starke. 2004;56:157–66.
13. Desai PM, Liew CV, Heng PWS. Understanding disintegrant action by visualization. J Pharm Sci. 2012;6:2155–64.
14. Abdelbary G, Eouani C, Prinderre P, Joachim J, Reynier JP, Piccerelle P. Determination of the in vitro disintegration profile of rapidly disintegrating tablets and correlation with oral disintegration. Int J Pharm. 2005;292:29–41.
15. Wohlfarth C. Permittivity (dielectric constant) of liquids. In: Lide DR, editor. CRC-The handbook of chemistry and physics. Boca Raton-Floride: CRC Press; 2004. p. 6–166.
16. Arnold WM, Gessner AG, Zimmermann U. Dielectric measurements on electro-manipulation medium. Biochim Biophys Acta. 1993;1157:32–44.
17. Yilmaz H. Excess properties of alcohol—water systems at 298.15 K. Turk J Phys. 2002;26:243–6.
18. Carmona-Garcia R, Sanchez-Rivera MM, Méndez-Montealvo G, Garza-Montoya B, Bello-Pérez LA. Effect of the cross-linked reagent type on some morphological, physicochemical and functional characteristics of banana starch (*Musa paradisiacal*). Carbohydr Polym. 2009;76:117–22.
19. Einstein A. Eine neue Bestimmung der Molekueldimensionen. Ann Phys. 1906;19:289–306. German.
20. Einstein A. Berichtigung zu meiner Arbeit: Eine neue Bestimmung der Molekueldimensionen. Ann Phys. 1911;34:591–2. German.
21. Senapati PK, Mishra BK, Parida A. Modeling of viscosity for power plant ash slurry at higher concentrations: effect of solids volume fraction, particle size and hydrodynamic interactions. Powder Technol. 2010;197:1–8.
22. Rubio-Hernandez FJ, Ruiz-Reina E, Gomez-Merino AI. An experimental study on the influence of a dynamic Stern-layer on the primary electroviscous effect. Colloids Surf A. 1999;159:373–9.
23. Kaunisto E, Rasmuson A, Bergenholtz J, Remmelgas J, Lindfors L, Folestad S. Fundamental mechanisms for tablet dissolution: simulation of particle deaggregation via Brownian dynamics. J Pharm Sci. 2013;5:1569–77.
24. Derjaguin BV, Landau LO. Theory of the stability of strongly charged lyophobic solutions and of the adhesion of strongly charged particles in solutions of electrolytes. Acta Physicochem URSS. 1941;14:633–62.
25. Genovese DB, Lozano JE. Contribution of colloidal forces to the viscosity and stability of cloudy apple juice. Food Hydrocoll. 2006;20:767–73.
26. Benitez EI, Genovese DB, Lozano JE. Effect of pH and ionic strength on disintegrant efficiency formula solubility juice turbidity: application of the extended DLVO theory. Food Hydrocoll. 2007;21:100–9.