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Sodium lauryl sulfate as lubricant in tablets formulations: is it worth?

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Abstract

Lubricants are excipients used in tablet formulations to reduce friction and adhesion forces within the die or on the punches surface during the manufacturing process. Despite these excipients are always required for the tablets production, their amount must be carefully evaluated since lubricants can negatively impact on mechanical strength, disintegration and dissolution behavior of solid dosage forms. Alternative compounds have been suggested to overcome the issues of conventional lubricants and sodium lauryl sulfate (SDS) is one of the most promising one. Despite SDS has been object of several investigations, a definitive conclusion on its effectiveness cannot still be drawn. Particularly, its efficacy on tablets disaggregation and API dissolution is still unclear. Here, the effect of SDS on all the relevant features of tablets and tableting process has been evaluated on immediate release hydrophobic tablets formulations in comparison with conventional lubricants. The results of this investigation are quite outspoken: SDS has a low lubricant power while it determines only a limited improvement on tablets hardness. It greatly improves the tablets wettability but only on model formulations, the presence of superdisintegrants resets its effectiveness and any possible effect on tablets disaggregation. None of the tested formulations showed improvement on the API dissolution rate.

Keywords: Lubrication, Sodium dodecyl sulfate, Magnesium stearate, Sodium Stearyl Fumarate, Contact angle, drug release.

1.Introduction

Lubricants are essential excipients for tablets manufacturing that operate by reducing the strength of adhesive interactions and kinetic friction forces between particles and metal surfaces, and consequently by favoring the process of tablet ejection from the die and the following scraping of it from the lower punches surface [1,2]. The reduction of the ejection and take off forces makes the overall powder tableting process much smoother, allowing the production of tablets without or with a low occurrence of the typical defects due to powder sticking within the die or on the punches surface. Today, the lubricants used in tablets manufacturing are the so-called “boundary lubricants”, constituted by solid materials having specifically features such as a low shear stress, a relatively high melting point, small particle size (consequently, large surface area), a certain amphiphilic activity, and a film-forming ability. These materials spread around drug and excipients powder particles creating a kind of non-continuous film, which reduces the friction forces during the compaction process [1]. Magnesium or calcium stearate, stearic acid, sodium stearyl fumarate and hydrogenated vegetable oils are the most common lubricants used for the formulation of commercial tablets [3]. Despite these excipients are always required in tablets formulations, they can have a negative impact on mechanical strength, disintegration and dissolution behavior. The last two aspects seem to be

related to the hydrophobic nature of the lubricants, which can obstacle (hinder) water penetration into tablets, thereby retarding the disintegration and dissolution process [4–8].

To overcome these issues related to the common "boundary lubricants", several others materials have been proposed and evaluated [9–13]. Among these, sodium lauryl sulfate (SDS) is surely the one attracted more interest, probably due to its chemical similarity with magnesium stearate in addition to its known abilities as wetting and dissolution enhancer agent. The literature data indicate that SDS possess a certain lubricant ability even if not comparable to that of classic lubricants, although it seems to positively affect tablets mechanical features [14–17]. Data on lubricant ability and on the effect on tablets mechanical resistance of SDS are generally convergent for all the investigations. The same cannot be said concerning the effect of SDS on tablets disintegration and drug dissolution. The effect of SDS on tablet disintegration is rarely reported and the few data available are not in agreement. Aly reports an improvement effect of SDS [16], while in other investigations it has been observed none or even negative impact [15,17]. Interestingly, de Backere et al. [17] reported an inverse correlation between lubricant hydrophobicity and disintegration time, in agreement with the "competition-for-water" hypothesis formulated by Ekmekciyan et al. [18]. The dissolution enhancement effect is often considered the main advantage for the use of SDS, and more in general, for the use of a surfactant lubricant in the formulation of solid oral dosage forms [19]. As such the European Medicines Agency (EMA) has identified SDS as a "Dissolution / wetting agent in solid oral dosage forms" [20]. Indeed, SDS, as well as many others water-soluble surfactants, is able to improve the drug dissolution rate through micellar solubilization [21] and, in some cases, also at concentration below the critical micelle concentration (CMC) through others mechanisms [22]. Nevertheless, a negative effect of SDS due to the formation of a less soluble salt or complex has been also reported for some drugs [23–26]. Although the effect of SDS as a solubility enhancer has been largely studied, its efficacy when used without any other lubricants is still debated and unclear. Indeed, the few published results are not in agreement, reporting an improvement of dissolution performance for celecoxib [15] and the opposite effect for ritonavir [24]. Other studies have focused exclusively on the dissolution enhancement ability of SDS in tablets lubricated with MgSt. Again, the results are not convergent, showing both a reduction [27,28] and an improvement [29] of the API dissolution rate. Now SDS is present, without others lubricant, in some tablets' formulations commercially available, as for example Aspro (500 mg acetylsalicylic acid tablets, Bayer S.P.A., IT) or Momentfene (600 mg Ibuprofen tablets, A.C.R.A.F. S.P.A, IT).

Literature analysis does not provide a definitive evaluation on the possibility of using SDS as tablets lubricant. Thus, with the aim to elucidate the real possibility of using SDS as lubricant, this surfactant has been employed as an alternative lubricant with the respect to some of the most common "boundary lubricants" as magnesium stearate and sodium stearyl fumarate. The study has been carried out on immediate release hydrophobic tablets formulations, using Acetaminophen or hydrochlorothiazide as model drugs and calcium hydrogen phosphate as filler. Acetaminophen and hydrochlorothiazide are APIs classified according to the European Pharmacopeia as sparingly soluble in water and very slightly soluble in water, representing good drug models to test the possible dissolution improvement due to lubricants. Calcium hydrogen phosphate was chosen as a filler since it is an insoluble compound commonly used in tableting process, known to generate high residual die wall stress and wall friction during tableting [30]. Therefore, it represents a good model material to test the lubrication attitude. The effect of the lubricant type has been evaluated in relation to the tableting process (lubrication ability) and to the features of the produced tablets (mechanical strength, wetting ability, disintegration and API dissolution).

2. Materials and methods

2.1 Materials

Acetaminophen was a gift from from Janssen Pharma. Sodium Stearyl Fumarate (Pruv®, JRS Pharma), croscarmellose sodium (Vivasol® JRS Pharma), sodium Starch Glycolate (Vivastar®, JRS Pharma) and

anhydrous calcium hydrogen phosphate (Emcompress Anhydrous, JRS Pharma), was donated by JRS Pharma, while Cross-linked PVP (Kollidon® CL, BASF Pharma) was donated by BASF pharma. Sodium Lauryl Sulfate (purity ≥ 98.5%) was purchased from Sigma-Aldrich, (St. Louis, MO, USA), magnesium stearate benzoic acid and hydrochlorothiazide were purchased from ACEF (Fiorenzuola d'Arda, IT)

Throughout the manuscript the materials are reported with the following abbreviations: acetaminophen (AAP), hydrochlorothiazide (HCT), benzoic acid (BA), magnesium stearate (MgSt), Sodium Stearyl Fumarate (SSF), Sodium Lauryl Sulfate (SDS), croscarmellose sodium (CCS), sodium Starch Glycolate (SSG), Cross-linked PVP (XPVP) and anhydrous calcium hydrogen phosphate (DCP).

2.2 Methods

2.2.1 Blends preparation and characterization

Blends constituted by a tablet filler (DCP, from 62 to 69%), an active pharmaceutical ingredient (AAP or HCT at 30%), a disintegrant (CCS, SSG or XPVP from 0 to 5%) and a lubricant (MgSt, SSF or SDS from 0 to 3%) were prepared using a V-shape mixer (Laboratori Mag Divisione Artha, Italy) operating at 50 rpm for 5 minutes. All the components were added together in the mixer except for the lubricant that was added at the end of the process, with an additional mixing time of 2 minutes. Additional blends were prepared using BA as active compound.

All the blends were characterized in term of real density using a helium pycnometer (AccuPyc 1330, Micromeritics, USA).

2.2.2 Tablets preparation and characterization

500 mg tablets were prepared from the blends using a 10-stations rotary tablet press (RONCHI, RIVA PICCOLA, Cinisello Balsamo, Milano, IT), equipped with flat faced round punches with a diameter of 11.28 mm and operating at 20 rpm. All the tablets were prepared setting the punch penetration to obtain a compression force of 25 kN (250 MPa).

For each batch of tablets, the compression and ejection forces were recorded. The tablets were characterized in term of hardness (TBH 30 hardness tester, Erweka, Langen, DE), thickness (Digital Caliper, Mitutoyo, JP) and weight. Tensile strength (TS) was calculated using the following equation:

$$TS = \frac{2 \cdot Hardness}{\pi \cdot Thickness \cdot \text{Diameter}} \qquad \text{eq. 1}$$

Tablets porosity was calculated as follows:

$$Porosity\ (\%) = (1 - D) * 100 \qquad \text{eq. 2}$$

Where D is the relative density calculated as the ratio of the tablet apparent density to the the powder pycnometer density.

2.2.3 Tablet wettability

The tablet wettability was examined by measuring the contact angle between the tablet surface and a 5 µL drop of deionized water. The wettability experimental set-up was build up in a manner similar to that proposed by Lamour et al. [31]. Specifically, the measurement was performed using a 12-megapixel camera (iPhone 13, Apple, USA) equipped with a 25x macro lens (SelvimTech, EU), positioned at 1 cm from the tablets. A beam of light generated by a fiber optic source (LE5214 and LE5210, Euromex, NL) passing through

an opaque glass has been used to light up the tablets to obtain good contrast. The schematic representation of wettability experimental set-up is shown a supplementary figure (**Figure SF1A)**.

For each tablet, a video has been recorded and frames were extracted at predetermined time intervals (an example of extracted frame is reported in **Figure SF1B**). All the extracted frames were analyzed through the ImageJ software [32] using the plugin "contact angle" (also known as Brugnara plugin) [33,34]. An example of the edge detection of such a plugin is shown in **Figure SF1C**. Each formulation was analyzed at least in triplicate.

2.2.4 Disintegration studies

Disintegration time (DT) was measured in deionized water using a disintegration test apparatus (Tecno Galenica, IT) operating at 37°C. Disintegration time was taken at the total disintegration of the tablets, that is when fragments can be no longer detected on the screen of the test tubes.

The disintegration times were determined analyzing 6 tablets of each formulation.

2.2.5 Dissolution studies

Dissolution tests have been carried out through a USP dissolution apparatus type II (AT7 smart, Sotax, CH) using 900 mL of deionized water as dissolution medium, maintained at 37°C and applying a paddle rotation speed of 50 rpm. Additional tests were carried out changing the paddle rotation speed from 50 to 100 and 200 rpm. Drug release was monitored spectrophotometrically (UV-1800, Shimadzu Corporation, JP) at the maximum wavelength of 242.5, 316 and 272.2 nm for AAP, HCT and BA APIs, respectively, at the following time intervals: 0, 5, 10, 15, 30, 45, 60, 90 and 120 min.

Each formulation was analyzed at least in triplicate.

3. Results and discussions

3.1 Effect of lubricants and disintegrants on tableting and tables features

The SDS lubrication power has been evaluated comparing the ejection force measured during the tableting cycle of AAP and HCT blends having all the same composition except for the lubricant type (MgSt, SSF and SDS) and amount (from 0 to 3% w/w). The results (**Figure 1** panels AAP_1 and HCT_1) clearly indicate marked differences between the lubricants. MgSt and SSF performed much better than SDS at all concentrations. Even at the highest concentration used (3% w/w), SDS is not able to fully match the performance of the other tested lubricants at 1% w/w, in agreement with the findings of Dun at al. [15]. According to these authors, the amount of SDS necessary to match the lubricant ability of 1% w/w MgSt could reach values up to around 5% w/w, as a function of the compaction mechanism of the formulation components (brittle component are much less sensitive to the lubricant type compared to deformable ones). The effect of the disintegrant (CCS) amount on the ejection force at fixed concentration of lubricant (3% w/w) has been evaluated as well. In this case, the results (**Figure 1** panel AAP_2 and HCT_2) suggest that the ejection force is not influenced by the CCS amount, at least when it is added at concentrations between 0 and 5% w/w, the normal range of use. According to these results, no interaction between CCS and lubricants on the ejection force can be supposed, in agreement with previous studies performed on stearic acid as lubricant [35,36].

Lubricants are essential excipients for tablet formulations, however, they usually lower the tabletability of powder blends [37,38], even if this effect appears much more pronounced in the presence of materials that respond to pressure mainly deforming (i.e. microcrystalline cellulose) rather than fragmenting (i.e. lactose or DCP) [1,15,39,40]. The results in **Figure 2** (panel AAP_1 and HCT_1) confirm the literature data, taking into account that AAP is an almost deformable material [41,42] while HCT is a brittle one [43]. The three lubricants

lower the tabletability in AAP formulations, while such effect is almost negligible when HCT was used. In this context, the use of SDS in the formulations containing some deformable materials (such as AAP) provides an improvement compared to MgSt but not versus SSF. The results about the comparison between MgSt and SDS are in agreement with Dun et al [15]. Instead, the performances of SDS and SSF have never been directly compared before, although it is reported that SSF usually has a lower impact on tablets hardness if compared to MgSt [1]. In the lower panels of **Figure 2** (panel AAP_2 and HCT_2), the effect of CCS is shown. CCS seems to influence in a positive manner the tensile strength of tablets containing AAP, independently by the lubricant type.

3.2 Effect of lubricants and disintegrants on tablet wettability

The effect of the lubricant type and the disintegrant (concentration and type) on wettability was evaluated measuring the contact angle between water and the tablet surface. Preliminary, the three different lubricants were compared each other at a constant concentration (3% w/w) using tablets prepared without the disintegrant. The results (**Figure 3**), demonstrated that SDS has a huge impact on tablet wettability, strongly reducing the interfacial tension with water, in comparison to tablets lubricated with MgSt or SSF. The differences were still more evident considering the kinetics of water absorption on tablet surface. In the presence of SDS, the droplet on the tablet surface almost disappeared after 4s, making the contact angle measurements at higher times practically impossible. Instead, in the case of MgSt and SSF, the water droplet slowly spreads on tablets surface and the absorption was slower. In these cases, the contact angle measurements were carried out up to 30 s, which is the maximum time up to which the droplet was analyzable, even if it is still visible for longer times (in some cases over 2 minutes). MgSt and SSF showed a similar behavior, with the latter characterized by a lower contact angle and thus a slightly better wettability. The different drugs had only a minimal effect on the contact angle measurements. These results are expected according to the nature of the different lubricants and also according to the previous findings published in the literature [15]. However, when the measurements were performed on more complex formulations, and specifically on those containing disintegrants, the results were surprising. In the presence of disintegrants, the droplets were absorbed much faster leaving at its place a kind of “solid bubble” constituted by dry swollen powder (**Figure 4**). This effect was described in 2021 by Markl et al [44] while observing sessile drop images in a study focused on the relevance of water absorption and swelling behavior in tablets disintegration. According to the authors, in presence of swellable materials (MCC and CCS), the interaction between tablets surface and water is characterized by in initial fast absorption phase (the duration was max 3-4 s) followed by a swelling process. Interestingly, the authors observed this sequence also in a formulation where the CCS (5% w/w) was the only swellable material, suggesting that the absorption/swelling process happens even in the presence of a small amount of swellable component, as observed in the present study. Here, the absorption/swelling process triggered by CCS has a huge effect on the duration of the water absorption and on the time evolution of the contact angle values. The absorption time (meant as the last time when the droplet is visible and analyzable on the tablet’s surface) showed an impressive reduction as the amount of CCS increased (F**igure 5**). For example, in the case of tablets containing AAP as API and MgSt as lubricant the addition of 1% w/w and 3% w/w of CCS determined a reduction of the absorption time of 18 and 46 times respectively. Again, the contact angle kinetics (**Figure 6**) also changed in a massive way. In this case, despite the initial value (t0) was practically unaffected by the presence of disintegrant, the contact angle values decreased very fast becoming impossible to be measured after few seconds. Both these effects were more pronounced on the formulations showing the worst wettability without CCS, namely those containing MgSt, and in a less extent, those containing SSF. The effect was also evident when SDS was used as lubricant, even if the absolute change of the absorption time and contact angle kinetics due to the CCS addition was much more limited. Therefore, it appears clear that the presence of CCS suppresses or reduces drastically all the differences in terms of wettability due to the different lubricant used.

To verify if this effect was specific of CCS or was a general feature of all the disintegrants, further tests were carried out using also the 1% w/w of SSG and XPVP as disintegrant in tablets lubricated with MgSt. The results (**Figure SF2**) indicated that all the superdisintegrants drastically improved the tablets wettability, making the water absorption kinetics almost overlapping.

3.3 Effect of lubricants and disintegrants on tablet disintegration

The contact angle measurements suggested that lubricants should not posses any influence on water absorption kinetics in the case that a disintegrant is present in a hydrophobic formulation. From a practical point of view, it means that the disintegration behavior should not be affected by the lubricant in presence of a disintegrant. The results of disaggregation tests (**Figure 7** upper panels AAP_1 and HCT_1) confirm this hypothesis. The tablets without disintegrant (containing a constant amount of lubricant at 3% w/w) remained intact during the test for more that 15 minutes; however, as the disintegrant was added, the disaggregation time felt at values below 20 s as a function of the CCS concentration. The type of lubricant did not show any influence on the process and the disaggregation time seemed controlled exclusively by the presence of the disintegrant. For a more detailed analysis, tablets containing 1% w/w of CCS were tested at increasing concentration of lubricants (**Figure 7** lower panels AAP_2 and HCT_2). Once again, the type of lubricant did not show any effect, while the concentration affected the process only in a marginal way (the maximum variation of disaggregation time was around 10 s).

These results clearly indicate that for immediately release hydrophobic tablets the use of a wetting agent or the substitution of a standard lubricant with a wetting agent does not improve the disintegration behavior and the reason is related to the effect of the disintegrant on the water absorption kinetic.

3.4 Effect of lubricants and disintegrants on API dissolution

Dissolution tests were performed to verify if the use of SDS in place of a hydrophobic lubricant can improve the dissolution behavior. The results (**Figure 8**) clearly showed that SDS has a negative effect on API dissolution for both the drugs tested, AAP and HCT, when compared with traditional lubricants. Interestingly, by increasing the basket rotation speed such differences were reduced up to almost disappear (**Figure 9A**), suggesting an effect related to the API dissolution rate.

The effect of SDS on API dissolution was initially unexpected; however, from a detailed analysis of literature, similar results were found. Zhao et al reported a negative effect of SDS on the dissolution of AAP and acetylsalicylic tablets [28]. The authors hypothesized that such effect was due to a reduction in tablets porosity because of the SDS addition, although they did not measure the tablets porosity. Differently, in the present work, the tablets porosity has been measured and it did not change in a relevant manner (**Figure SF3**) when MgSt or SSF are substituted by SDS. Therefore, the hypothesis of Zhao et al. appears to be unlikely at least for the present results. Another possibility to explain the slowing effect of SDS on the API release has been proposed by Guo et al by studying the release of ritonavir tablets [24]. The authors observed a reduction of API release when the SDS concentration was lower than its critical micelle concentration (CMC), due to the formation of a API-SDS salt with a lower solubility respect to the API alone. However, when the SDS concentration was higher than CMC the dissolution rate increased markedly. To verify this hypothesis further dissolution tests were performed by adding SDS in the dissolution media at a concentration above the CMC (CMC 6.5-9.2 mM [45], concentration used 20 mM). The results, (**Figure 9B**), did not show any significant differences on AAP release, even when SDS is present in the medium as micellar aggregates. Finally, it has been verified the hypothesis related to the formation of a lower solubility salt or complex between APIs and SDS. Such possibility has been reported also by Bhattachar et al for trimethoprim and for an unspecified basic compound [25], by Desai et al for metformin [23], and by Huang et al for a not defined cationic drug [26]. In all cases, the drugs involved in the salts formation were weak bases as in the case of AAP and HCT studied in the present work. To prove the hypothesis of the formation of an insoluble salt/complex it has been replicated the test carried out by Guo et al using ritonavir tablets [24]; different amounts of SDS were added to an AAP solution and the presence of turbidity was monitored after each addition. The test has been performed using a concentration of AAP equal to 150mg/900ml (the highest concentration used for the dissolution test). In addition, such tests were repeated also using higher concentration of AAP. In no case turbidity was observed. From the other side, when the same experiments were repeated by changing the AAP with calcium chloride an immediate formation of a turbid dispersion occurred, due to the presence of the insoluble salt calcium lauryl sulfate. The hypothesis of the formation of a low solubility complex is also

unlikely from a stoichiometric point of view. In fact, the molar ratio between APP and SDS in the present study is equal to 5.2; so, even if a soluble salt was formed, no more than the 20% of the active compounds should be involved (the most likely stoichiometry ratio for the salt is 1:1). Consequently, salt formation could not explain the differences observed, especially in the first time points of the dissolution profiles; in fact, in the first three time points (t10, t15 and t30) the amount AAP released from MgSt tablets is at least the double of that released from SDS tablets. For a further corroboration of the impossibility of the salt formation, the dissolution behavior of an acid model drug, the benzoic acid (BA), formulated in tablets lubricated with MgSt or SDS has been studied. This compound should not form any salt with SDS (both are acid compounds); however, also in this case, the BA release rate was still slow down by the presence of SDS (**figure 9C**).

4. Conclusions

SDS has been tested as an alternative lubricant with the respect to MgSt and SSF, by evaluating its impact on the ejection process during tableting and on the tablet's characteristics (mechanical properties, disintegration ability and API's dissolution behavior). SDS assures a modest improvement of the tabletability, despite its poor performance in term of lubricant power. It shows a relevant wetting effect exclusively on model tablet formulations without disintegrant. The presence of a disintegrant resulted to suppress the effect of SDS on tablet wettability, being the only excipient influencing the water absorption kinetics as well as the disintegration phenomenon. None of the tablets lubricated with SDS showed any improvement in term of API's dissolution, even resulting in a lowering of the drug dissolution rate.

The results of this investigation are quite outspoken not supporting the use of this compound in tablet formulation.

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Legends of Figures

Figure 1. In the upper panels it is shown the effect of the lubricant type and concentration (0-3 %) of formulations containing a constant amount of CCS (1%) and AAP (panel AAP_1) or HCT (panel HCT_1) as API on the ejection force. In the lowers panels it is shown the effect of the lubricant type and CCS concentration of formulations containing a constant amount of lubricant (3%) and AAP (panel AAP_2) or HCT (panel HCT_2) as API, on the ejection force.

Figure 2. In the upper panels it is shown the effect of the lubricant type and concentration of formulations containing a constant amount of CCS (1%) and AAP (panel AAP_1) or HCT (panel HCT_1), on the tablet tensile strength. In the lowers panels it is shown the effect of the lubricant type and CCS concentration of formulations containing a constant amount of lubricant (3%) and AAP (panel AAP_2) or HCT (panel HCT_2), on the tablets tablet tensile strength.

Figure 3. Effect of lubricant type (at a concentration of 3%) on the contact angle kinetics in tablets containing AAP or HCT as API. The disintegrant is not present in the tablet formulations.

Figure 4. Visual comparison of the kinetics of the drop absorption in tablets without (0% CCS) and with disintegrant (3% CCS). The images refer to the formulations containing AAP as API and 3% of SSF as lubricant.

Figure 5. Effect of the CCS amount on the droplet absorption time in presence of different lubricants (3%).

Figure 6. Effect of lubricant type (at a concentration of 3%) and CCS concentration on the contact angle kinetics in tablets containing AAP or HCT as API.

Figure 7. Effect of the CCS amount on the disintegration time of tablets prepared with the three different lubricants (3%) for the two API studied (upper panels). Effect of the lubricant amount on the disintegration time of tablets prepared with the three different lubricants and 1% of CCS for the two API studied (lower panels).

Figure 8: Effect Effect of the lubricant type (3%) in AAP or HCT tablets containing 1% of CCS**.**

Figure 9: A) Effect of paddle rotation speed on the dissolution behavior of AAP tablets containing 1% w/w of CCS and 3% w/w of lubricant (MgSt or SDS). **B)** Effect of SDS in the medium (concentration higher than its CMC) on the dissolution behavior of AAP tablets containing 1% w/w of CCS and 3% w/w SDS. The curve of MgSt tablets was added for comparison. **C)** Effect of lubricant type (3% w/w) on the dissolution behavior of AAP or BA tablets containing 1% w/w of CCS.

CRediT authorship contribution statement

Beatrice Sabbatini: Investigation, Formal analysis, Writing - original draft. Diego Romano Perinelli: Methodology, Data curation, Writing - review & editing. Giovanni Filippo Palmieri: Supervision. Marco Cespi: Conceptualization, Data curation, Writing - original draft. Giulia Bonacucina: Supervision, Writing -review & editing.

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐ The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Figure 1

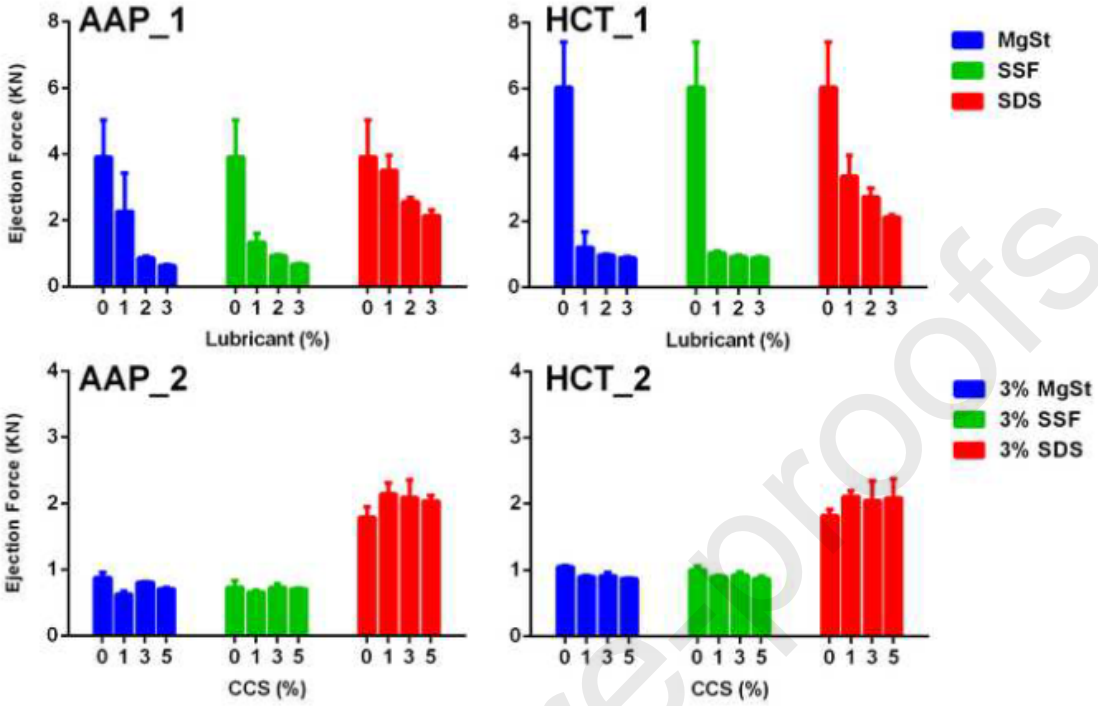


Figure 2

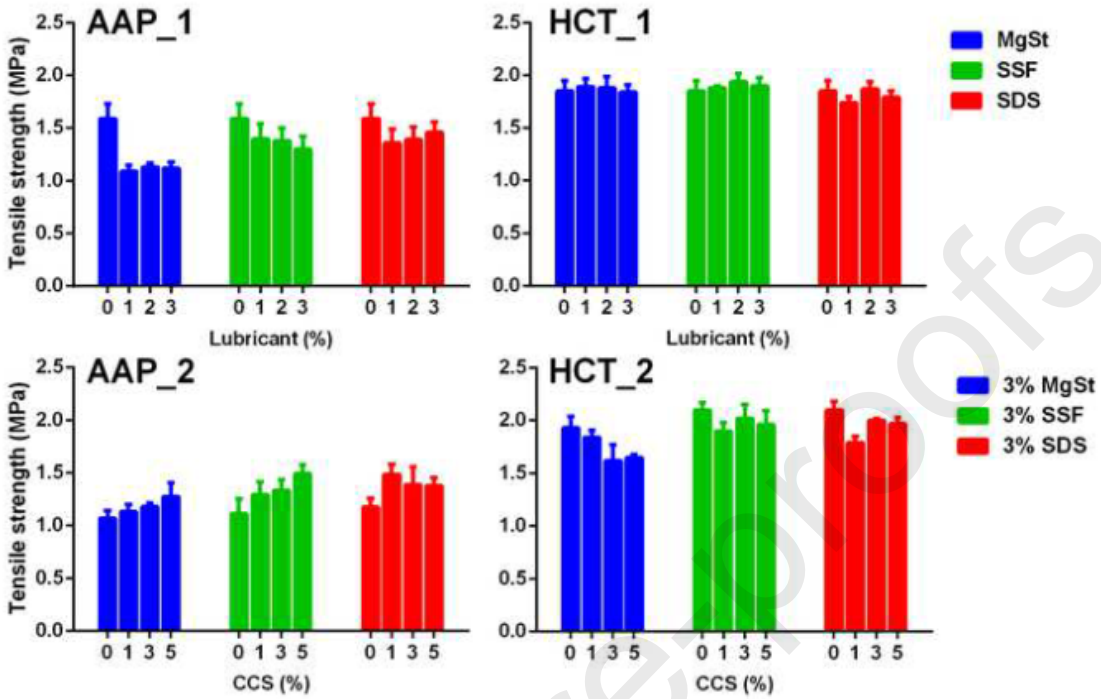


Figure 3

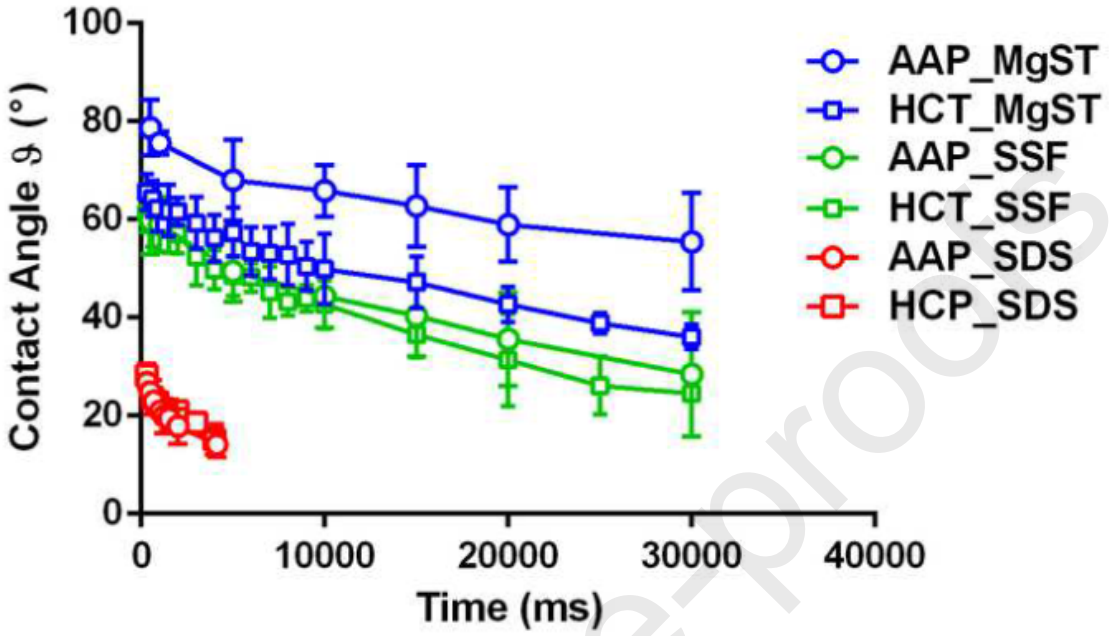
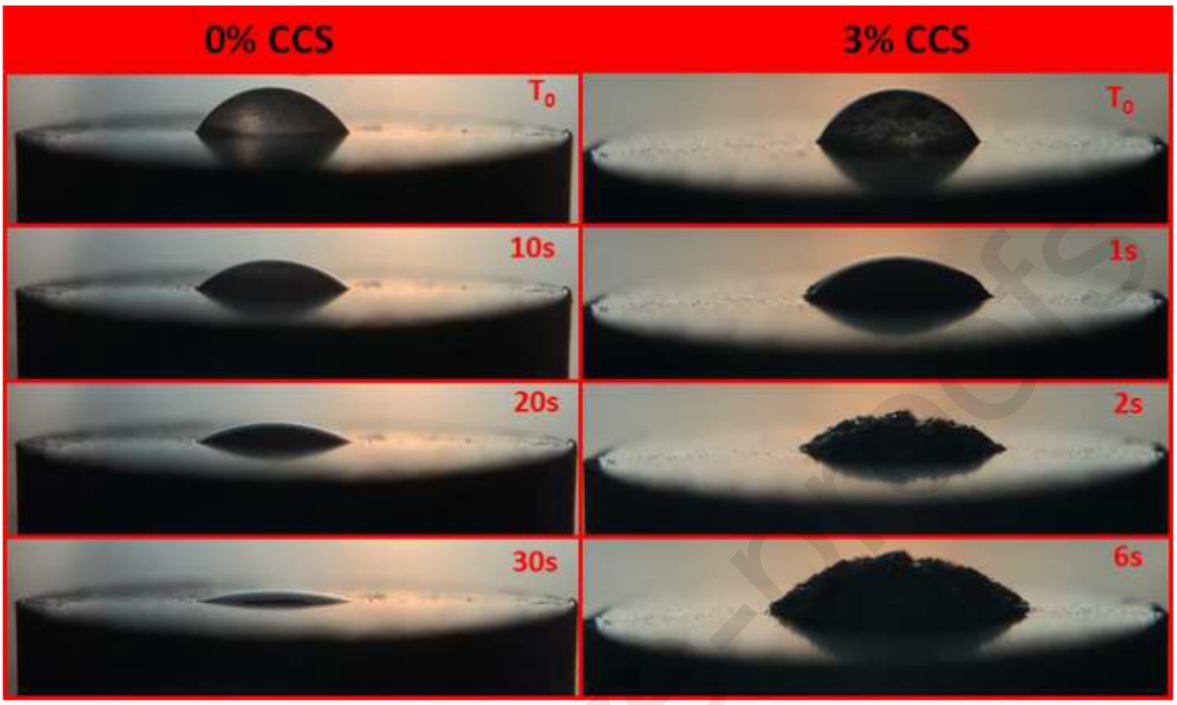


Figure 4



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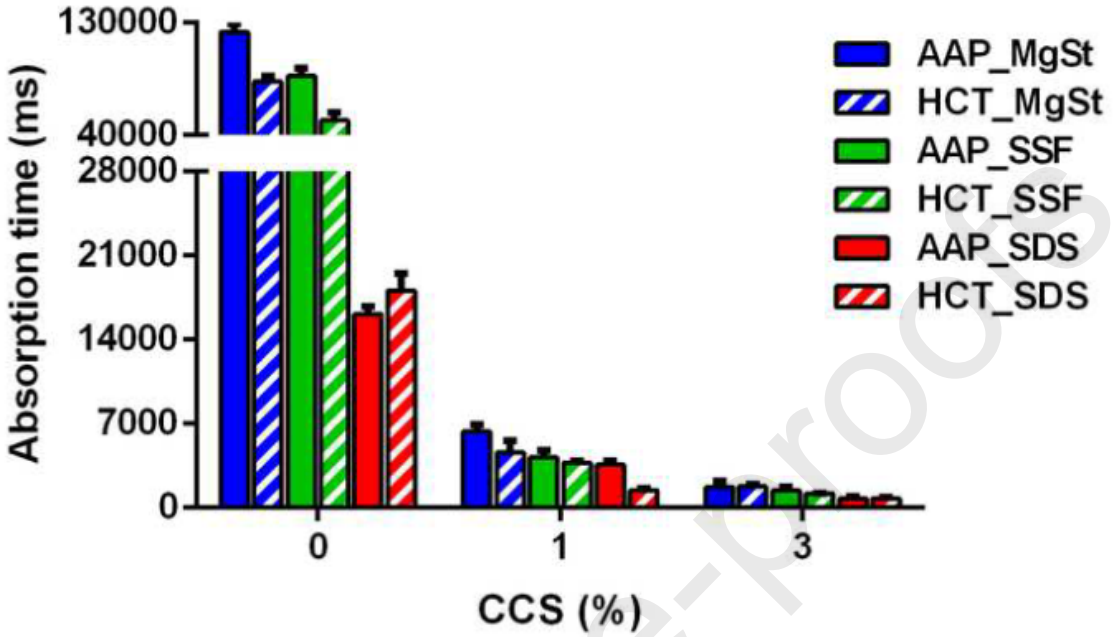


Figure 6

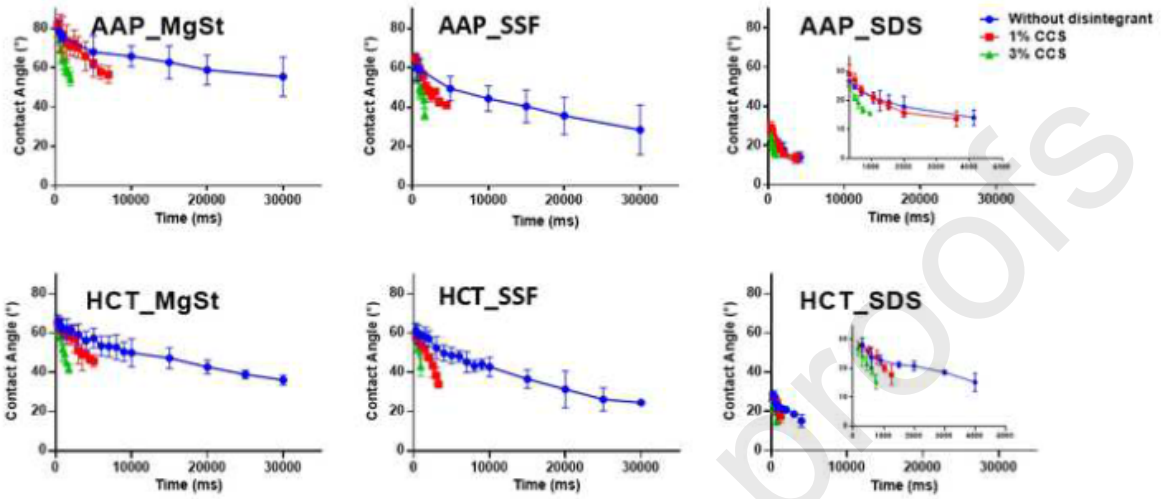


Figure 7

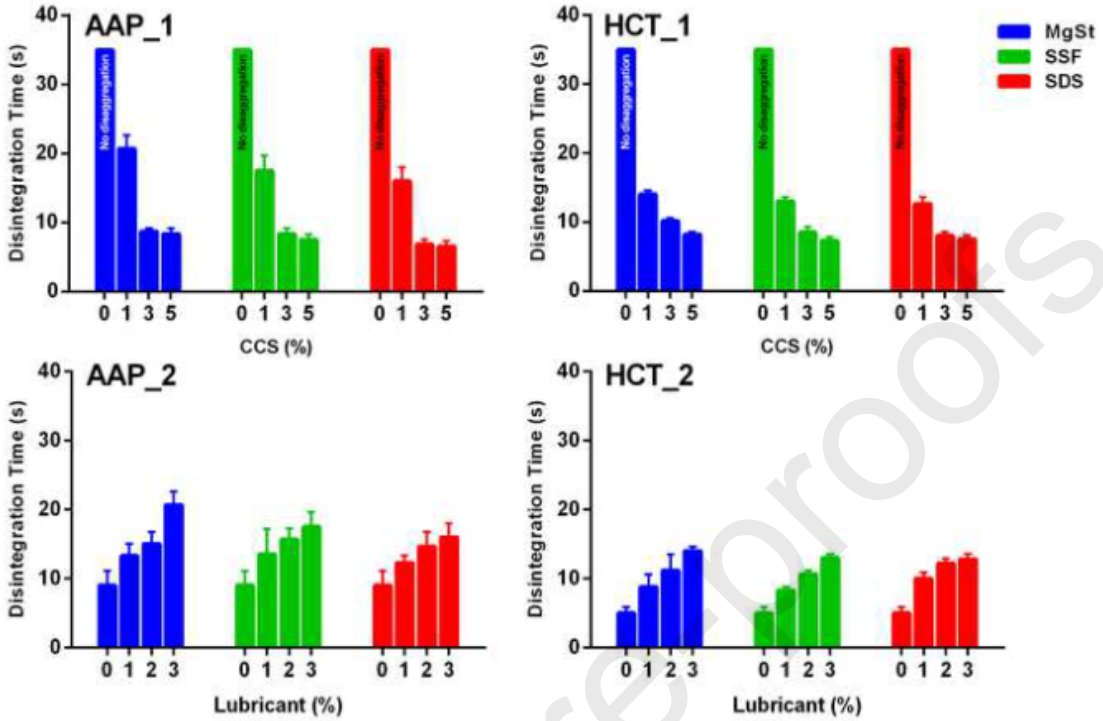


Figure 8

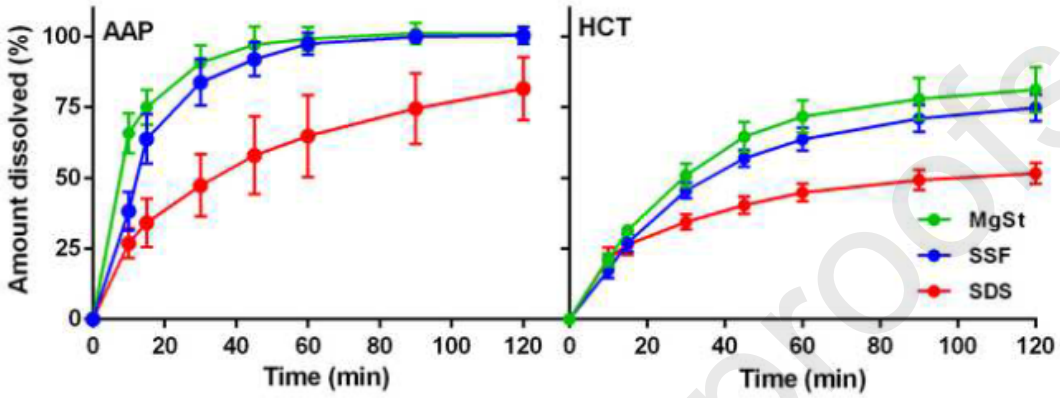
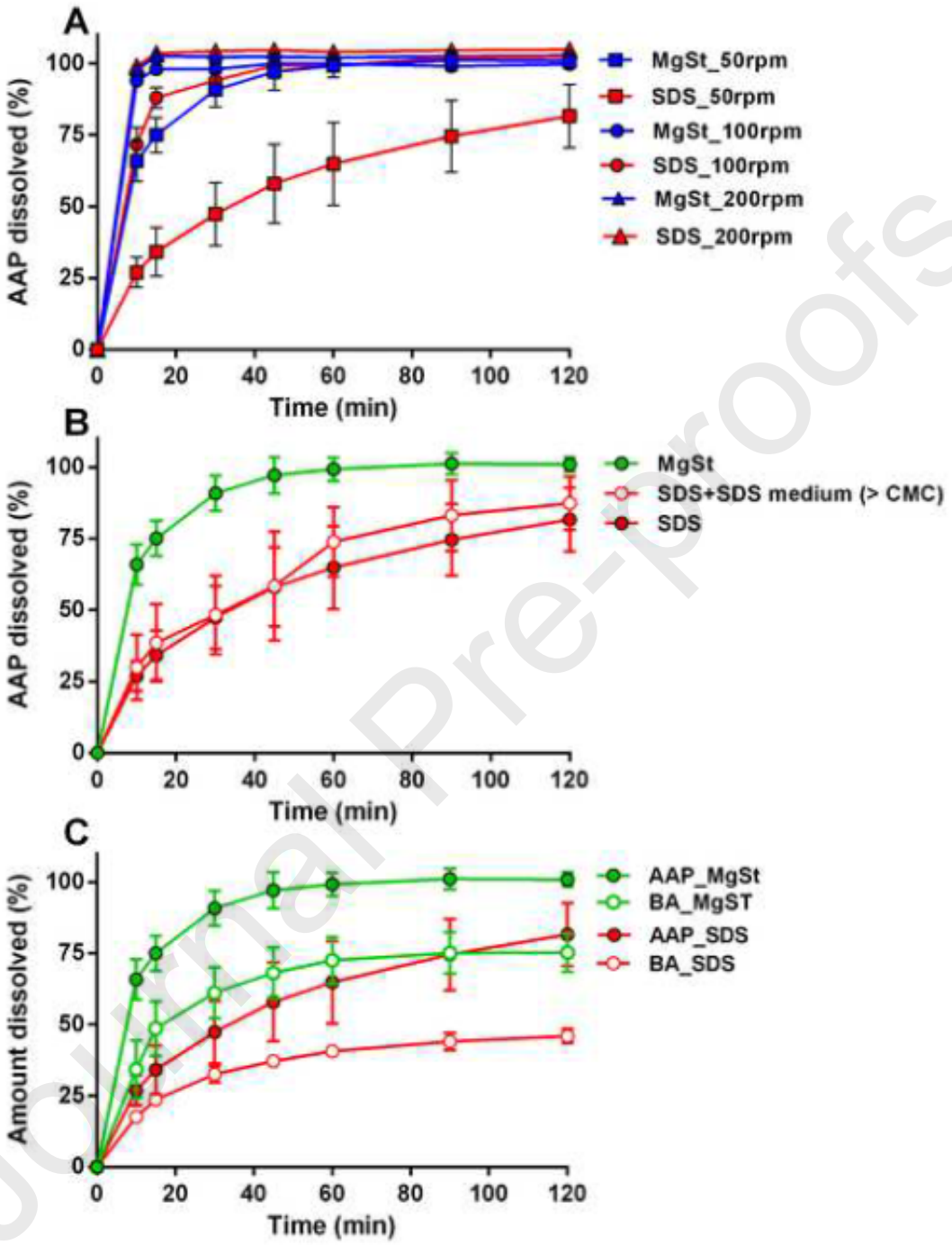


Figure 9



Graphical Abstract (for review)