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Research paper

New processing technique for viscous amorphous materials and characterisation of their stickiness and deformability

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ABSTRACT

This paper reports on a technique using ultrasound-assisted equipment to characterise and handle stickiness of viscous amorphous blends of citric acid and paracetamol after melt mixing and during processing. Deformability and stickiness were studied using a specially designed sample measurement compartment. An ultrasound-assisted nozzle and knife for pharmaceutical applications were studied. The application of ultrasound was found to increase the mass flow through a nozzle connected to a pressurized tank. This effect was found to be separate from the increased mass transport resulting from the reduced viscosity as the temperature was increased. Ultrasound was also found to have a favourable influence on cutting through melt extrudates. The stickiness and resistance to deformation of samples were observed to be dependent on the amount of paracetamol in the blend and temperature that was in agreement with the glass transition temperature and viscosity. Other influencing factors, such as time-dependent wetting and surface energetics, are discussed. We conclude that it is possible to characterise stickiness and resistance to deformation of viscous amorphous materials with a specially designed probe test, and the stickiness of amorphous material can be handled during processing with ultrasound-assisted equipment.

1. Introduction

Poor solubility of the drug may decrease the pharmacological activity of the active pharmaceutical ingredient due to its poor absorption rate [1]. Thus, researchers are studying different methods to increase the solubility of the drug such as preparing the drug into an amorphous form, which has a better solubility than the crystalline form. One problem in the pharmaceutical industry is the absence of a proper large-scale processing method to produce amorphous drugs [2]. In addition, there are some difficulties in developing a solid dosage form with high drug load in a single preparation. Amorphous drugs or amorphous solid dispersions might have lower glass transition temperatures (T_gs) than ambient temperature. Thus, processing such materials into a solid dosage form might be challenging due to their soft and sticky nature. To prepare a 25 mg indomethacin solid dispersion tablet, for example, it demands approximately 600 mg excipients [3]. In addition, solid dispersions have processing problems because they are usually sticky and hygroscopic [4]. Even after the development of a proper manufacturing method there are still some problems. For instance, many processing operations may trigger the crystallisation process during manufacture of the solid dosage form [5,6].

Ultrasound (US) is proposed as a promising method to increase the flow of sticky and highly viscous material in the food industry [7]. In addition, ultrasound cutting blades can be used for cutting cheese, candy, bakery, confectionary, and convenience foods [8]. Low frequency ultrasound varying typically from 20 to 50 kHz is used widely in the food industry. High frequency US from 1 to 10 MHz is being used for diagnostic purposes. Ultrasound can also be divided into low intensity and high intensity US [9]. Power in the low intensity US is less than 1 W cm^2, and it is used mainly for analytical methods. High intensity US uses power levels ranging from 10 to 1000 W cm^2, and it is used mainly for the physical and chemical treatment of the material.

So far, researchers have been interested in drugs having a higher T_g than ambient temperature, because drug systems having a low T_g are thought to be physically too unstable and difficult to handle/process in an industrial scale. One problem in the processing of supercooled melt into a solid dosage form is the lowered viscosity that is related to the stickiness of the drug that makes common unit operations used nowadays hard to use. Previous

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research selected a blend of melt produced 50/50 (w/w, %) paracetamol (PARA) and citric acid anhydrate (CAA) blend as a model system for processing [10]. In this study, material properties such as stickiness and deformability, a new processing technique for this kind of sticky amorphous model system was developed and studied [11], and a low frequency ultrasound-assisted nozzle and knife for pharmaceutical application were used and tested.

2. Materials and methods

2.1. Material properties

The material properties such as deformability and stickiness of the samples were probed using a LLOYD material tester (Lloyd LRX, Lloyd instruments Ltd., Fareham Hampshire, Great Britain) with a specially designed sample measurement apparatus. The purpose of the measurement was to test material deformability in compression and to test the stickiness of the material in decompression. The design of the experiment was a full factorial-interaction model as presented earlier [10]. Melt-quenched samples containing citric acid and paracetamol with five different compositions were poured on a four/five hexagonal nut (Ø 10 mm, 7 mm deep) that was used as a sample holder in the LLOYD material tester. The nut was screwed into a sample holder, which was covered with a transparent sample compartment. Heated air was used to control the temperature in the sample compartment (humidity at gas line was 5 ± 1%, RH at 25 °C). Five different measurement temperatures were used 25, 30, 35, 40 and 45 °C. The temperature probe was installed in a drilled hole under the nut. The temperature was equilibrated five minutes before measurement; the variation in temperature during measurement was ±0.2 °C. The diameter of the flat steel punch was 5 mm. The punch was pushed into the sample 5 mm and after that pulled off. If a load limit of 90 N was achieved, the punch was automatically pulled off the sample. Preload in contact was 0.5 N, and the driving speed of punch was 3 mm/min in decompression and compression. The compression and decompression force of the punch was measured. Resistance to deformation was evaluated from the compression curve calculating the slope of compression (N/mm). Stickiness was evaluated from the minimum force (N) measured in the decompression curve. This kind of measurement setting involves shear, compression, and extrusion [12].

2.2. Ultrasound-assisted processing

2.2.1. Technical information

The input of ultrasonic power was adjusted using an ENI Model 1104LA amplifier, and the frequency was set using an Aitrel/American Reliance Inc. function generator Model FG-506. Langevin-type piezoceramic sandwich transducers were used in both the US nozzle and the US knife.

2.2.2. Materials and sample handling before measurement

The model material was a 50/50 (w/w, %) paracetamol and citric acid blend. In the melting, the batch size was 100 g. Melting time was 6 min at 179 ± 2 °C with settings similar to those described elsewhere [10]. The melt sample was poured in a cylinder (Ø 30 mm) and cooled at room temperature (cooling time approximately 3 h). Initial extrapolated T_g^{mid} (midpoint) of the blend was 15.3 ± 0.2 °C. The samples were held in dry condition (silica desiccator) overnight after which pre-melting was done in a pressurized sample tank before the experiments (Fig. 1). Stabilizing the temperature of the model material according to the experiment temperature (50, 60 and 70 °C) took approximately 50 ± 10 min.

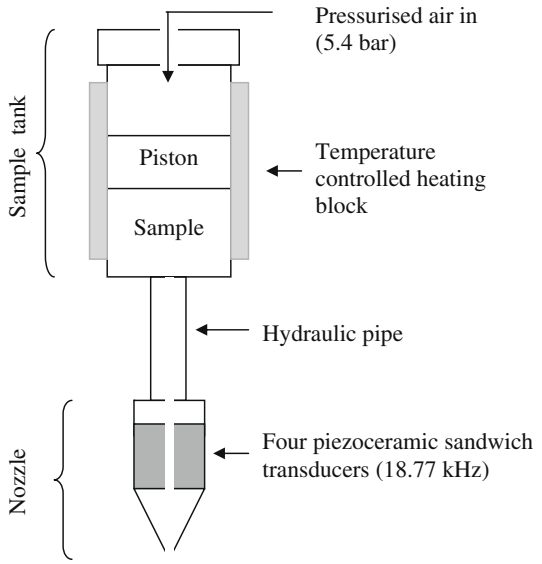

Fig. 1. Schematic cross-section representation of the ultrasound equipment used in the experiments (not in scale). The nozzle and hydraulic pipe were heated with hot air. To control the temperature of the sample, a temperature probe was set inside the wall of the sample tank; the temperature of the sample was also controlled during the pre-melting.

2.2.3. Design of the ultrasound-assisted nozzle

The ultrasound nozzle is presented in Fig. 2. It was constructed to give the maximum ultrasound amplitude in a longitudinal direction. The nozzle system was insulated from the sample tank with a hydraulic pipe. This was because the connection to the sample tank could dramatically change the working frequency of the US nozzle. Frequency used in the nozzle was 18.77 kHz.

2.2.4. Ultrasound-assisted extrusion

The design of experiments was a full factorial-interaction model with 11 experiments and 9 duplicates (total of 20 experiments). The factors included: the ultrasound power (0, 50, 100 and 150 W) in the nozzle and temperature (50, 60 and 70 °C) of the material in the sample tank and in the ultrasound nozzle. The experiment at 150 W and 70 °C was not done due to rapid mass flow. Pressure in the chamber during extrusion was constant (5.4 bar). The ultrasound pulse during the mass flow was 60 ± 5 s, and pulses used during the experiment changed from 3 to 5 (see

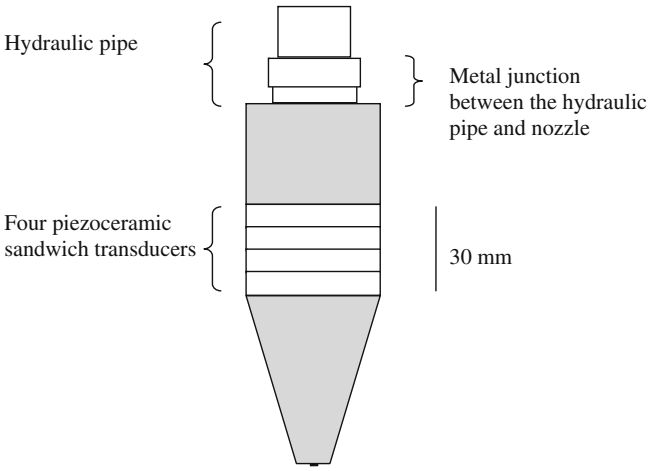

Fig. 2. Schematic representation of the ultrasound nozzle (in scale). The weight of the nozzle was approximately 200 g.

Fig. 7a). The ultrasound nozzle warmed up at the metal junction between nozzle and hydraulic pipe when the US power was switched on. The metal junction was cooled with an air cooler, which cooled down the junction to operation temperature. With the help of ultrasound pulsing, the effect of the warm-up of the nozzle on the mass flow could be evaluated.

2.2.5. Ultrasound-assisted cutting

Extrudate was forced through a 3 mm (diameter) orifice and collected on a paper sheet. Extrusion temperature was 50 °C, and US power was not used in the nozzle. After extrusion, the extrudate was warmed up to 40, 50 and 60 °C with a hot air. After heating, an ultrasound knife was used to cut the extrudate into pieces (Fig. 3). In addition, cutting was tested at 25 °C. The US knife was operated at a frequency of 24.89 kHz. The power levels used were 0, 50 or 100 W. The knife was cooled down with an air cooler during the cutting process. String cutters were only used for in-line cutting. In-line cutting was only performed at a power of 50 W.

2.2.6. Statistical methods

The design of the experiments and data analysis were done with a multilinear regression method (Modde, ver. 7.0, Umetrics AB, Umeå, Sweden). Curve fitting procedures were done using Origin software (Origin 7.5, OriginLab Corporation, MA, USA).

3. Results and discussion

3.1. Relationship between stickiness, deformability, glass transition and viscosity

Stickiness and material tactile properties can be characterised with direct measurement methods, such as various probe tests, or with indirect methods, such as evaluation of the glass transition [13,14]. An example of our recorded force–deformation curves of a 50/50 (w/w, %) sample is presented in Fig. 4. Fig. 4 shows the temperature-dependence of resistance to deformation in compression, and minimum force in decompression. Raising the measurement temperature decreased the resistance to deformation (N/mm) in all amorphous samples (Figs. 4 and 5a). A high PARA ratio in the composition increased the resistance to deformation, as seen in the resistance to deformation results in Fig. 5a. This is the result of the more rigid structure of PARA in comparison with CAA, as reflected in the difference in T_g and viscosity [15]. Even small amounts of CAA have been observed to decrease shear viscosity and increase fluidity of polymer blends [16], which will increase deformability. Pure melt produced CAA was partly crystalline during the test (as indicated directly afterwards with a XRPD) [10], and

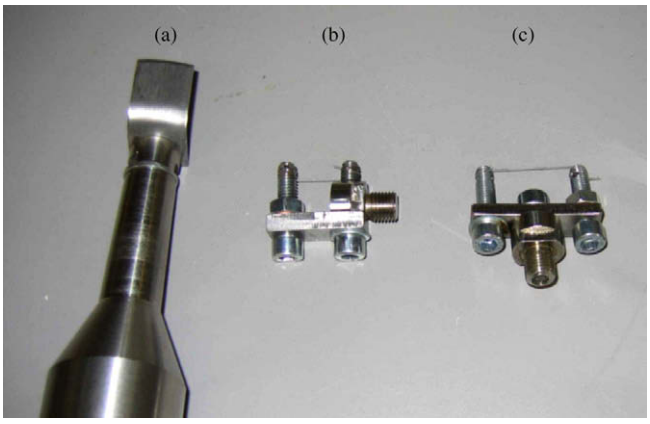

Fig. 3. Ultrasound knives used. (a) Knife or (b) and (c) string cutters.

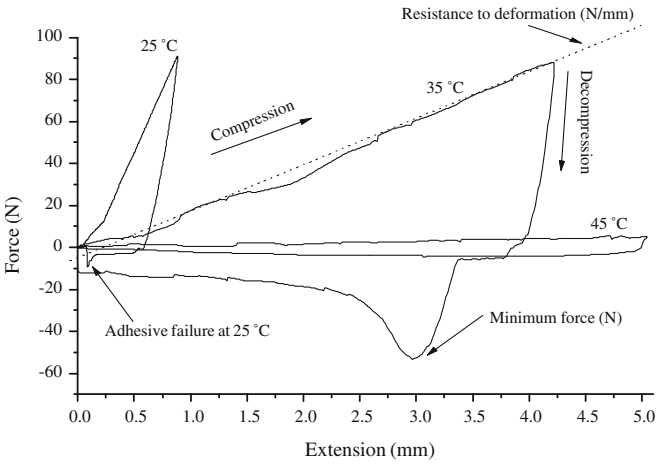

Fig. 4. Example of compression and decompression forces (N) for a 50/50 (w/w, %) sample as a function of extension depth (mm) measured at different temperatures (25, 35 and 45 °C). Furthermore, fitting of deformability (N/mm) is shown as a dotted line, and minimum force refers to the stickiness of the sample.

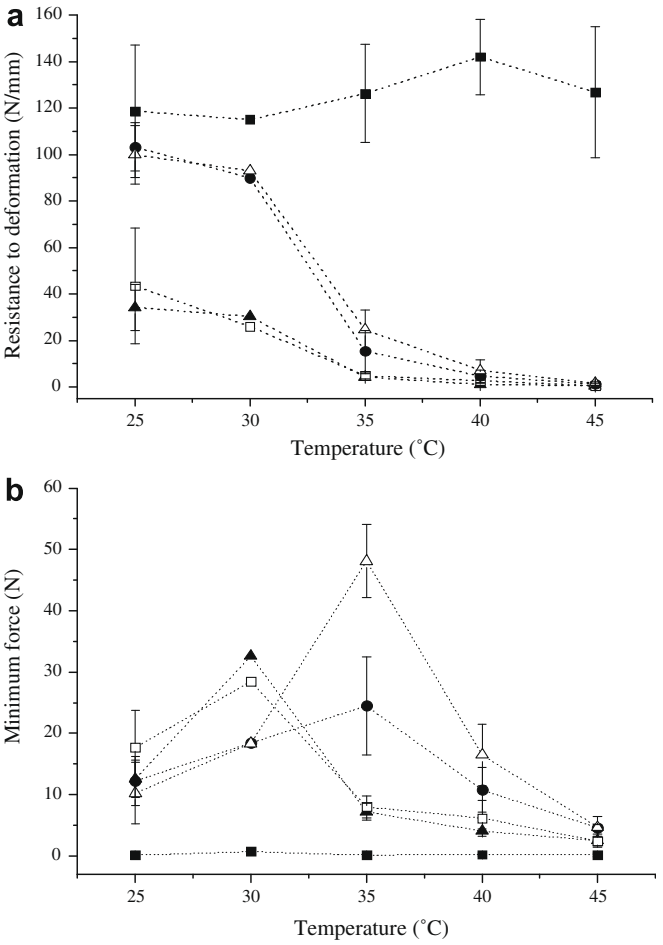

Fig. 5. (a) Resistance to deformation (N/mm) and (b) absolute values of minimum force during decompression (N) imitating stickiness of the sample as a function of the measurement temperature (°C). The labels are CAA (▲) (extrapolated T_g midpoint, T_g = 14 °C, partly crystalline sample), PARA (■) (crystalline sample), PARA50 (●) (T_g = 17.9 °C), PARA25 (□) (T_g = 14.7 °C) and PARA75 (Δ) (T_g = 21.3 °C) (T_g Stdev. approx. 1.3 °C). The dotted lines are shown as a visual aid, and the error bars are the standard deviation (n = 5 or 6) (n = 1 at 30 °C).

the crystallinity might have increased the measured deformability. Processing method, i.e. melting time and melting temperature of the sample, had no effect on the measured resistance to deformation when analysed by multilinear regression method.

The failure mechanism [17] between the punch and the amorphous material in decompression was adhesive (clean punch surface with no surface residues) rather than cohesive (residues on punch surface) in decompression at 25 °C (Fig. 4). In contrast, at temperatures higher than 25 °C cohesive failures were more dominant. Cohesive failure has been reported to increase at the high temperature due to the changes in viscosity [17]. Stickiness was affected by the amount of PARA in the composition and the measurement temperature (Fig. 5b). In this study, the highest decompression forces were measured at 35 °C for samples containing 50% (PARA50) and 75% PARA (PARA75). All the other samples achieved the highest decompression force at 30 °C (except crystalline PARA, which was not sticky).

In addition to viscosity, stickiness and adhesion are linked to surface tension (driving force for flow) [18] and surface energy [19]. Pharmaceutical manufacturing equipment is usually made of steel and, as seen in our probe test, stickiness may be a problem. Steel has extremely high surface energy, and thus good wetting is achieved easily with adhesives such as polymers, which usually have low surface energies [19]. Continuous contact between the punch surface and sample through wetting is an important mechanism for achieving good adhesion [19]. Wetting of the punch surface with amorphous material might take a longer time than the experimental time scale because of the increased viscosity at low temperatures. Thus, stickiness is also a time-dependent phenomenon [18,20]. The viscosities of our samples varied from 4.6 E+07 Pa s (10 °C above T_g^{mid}) to 1.1 E+06 Pa s (20 °C above T_g^{mid}) calculated by the Vogel–Tamman–Fulcher model [15].

Stickiness can also be characterised by indirect measurement methods, which include the glass transition temperature [14]. The sticky point of amorphous sugars is reported to be from 10 to 20 °C higher than the glass transition temperature (onset) [21,22]. This is because amorphous material is changed from a glassy to a viscous liquid state at higher temperatures than T_g, which is related to stickiness [22,23]. During storage, stickiness may occur at temperatures lower than glass transition onset (T_g^{ons}) + 10 °C due to the long contact time during storage, but it does not occur below T_g^{ons} [22]. The sticky point in our study (minimum force at decompression) was approximated to be 10–15 °C higher than the T_g^{mid}, which agrees well with other studies [21,22,24]. Stickiness decreases considerably when the measurement temperature is approximately 20 °C higher than T_g (Fig. 5b). A small amount of crystallinity in the CAA sample may increase adhesion and cohesion (see Ref. [10]). A small amount of needle-like crystals in an amorphous matrix may strengthen the structure of the sample against the decompression force. This kind of behavior has been reported in polymers [19].

3.2. The effect of ultrasound power on mass flow

The effect of ultrasound power (W) as a function of temperature (°C) on the mass flow (g/s) is shown in Fig. 6. It can be seen that the mass flow improved as the mass temperature or ultrasound power was increased. The increased mass flow was not related to the warm-up of the nozzle in our study. This is because the weight of the nozzle is approximately 200 g, and it needs a great deal of heat to warm-up. Secondly, mass flow increased instantly when US power was switched on (60 s pulse), while mass flow decreased immediately after the power was switched off (Fig. 7a).

Ultrasound power had a higher effect on the mass flow when the mass temperature was high. Similar results have been described in polymer extrusion; US has been observed to improve

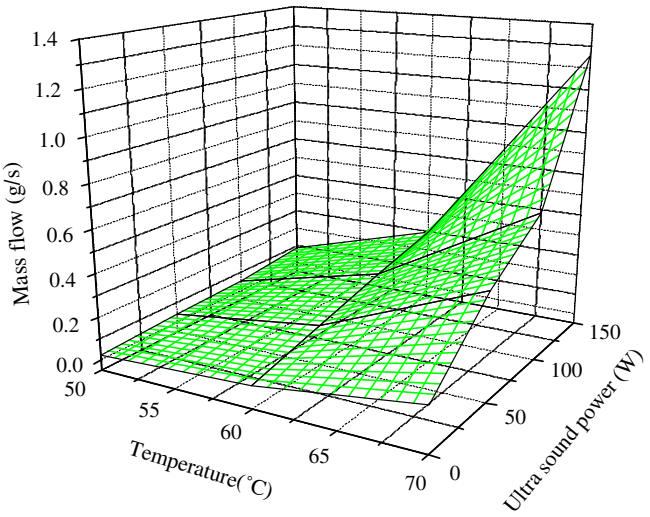

Fig. 6. The effect of ultrasound power (W) as a function of temperature (°C) on mass flow (g/s) ($Q^2 = 0.89$, $R^2 = 0.92$). Values calculated from the average of the whole mass flow (g) vs. time (s) curve. Complex viscosities of 50/50 blend samples are approximately 50.1×10^3 Pa s at 50 °C, 5.3×10^3 Pa s at 60 °C and 0.9×10^3 Pa s at 70 °C [15].

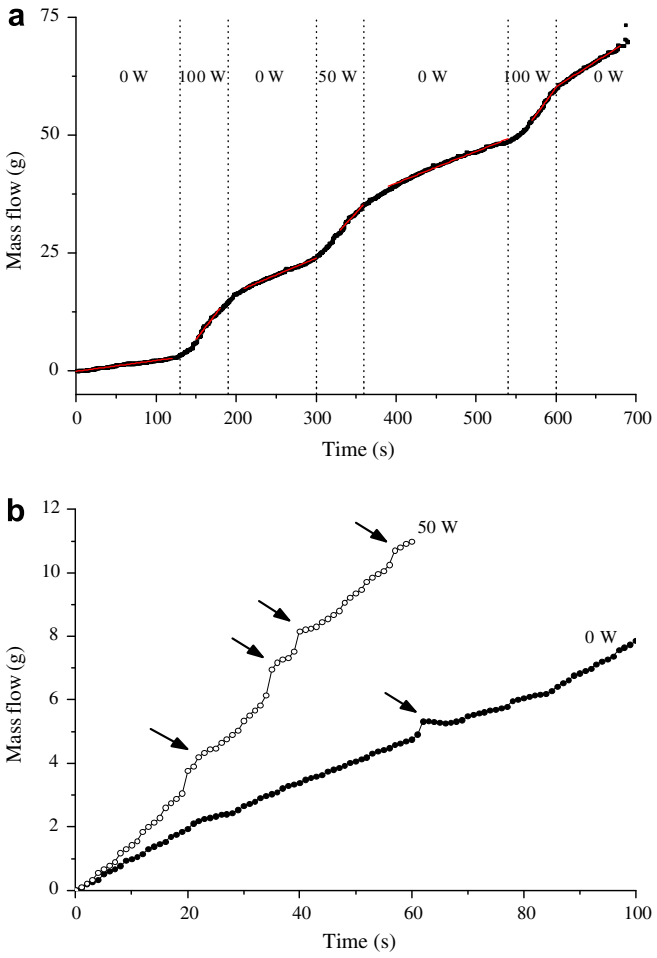

Fig. 7. Effect of US power (W) on mass flow and breakdown of extrudate at 60 °C with 5.4 bar pressure. A large number of bubbles were observed in the extrudated mass. (a) Total mass flow (g) as a function of time (s) and different ultrasound pulse series used. (b) Effect of US power 0 or 50 W on the mass flow in the nozzle. Arrows in (b) show disturbance in the mass flow recorded by the balance due to the breakdown of the extrudate.

the rheological and processing capabilities of polymers [25]. The main reasons were thought to be a slight decrease in the viscosity, and a reduction in the surface stress (friction) between metal and melt in the nozzle. These phenomena will decrease the die pressure, which has been reported in many extrusion studies of polymers [26,27]. Thus, US is observed to lower the die temperature needed in the extrusion process (approximately 30 °C) [25] and allowed processing at mild temperatures. A lowered processing temperature will also reduce costs due to lowered energy requirements. In addition, US is observed to increase the die durability and to produce a smoother surface on the extrudate [27].

Van Hook and Frulla [28] reported that acoustic waves damped rapidly in supercooled melts and in sugar syrups. There are many possibilities why US attenuates in material. The main causes are adsorption and scattering of US [9]. Some of the ultrasound energy is always transformed to heat due to adsorption, which is mainly dependent on the material properties. This increase in temperature might have an effect on the chemical stability. Boundaries and inhomogeneity of the sample may also involve sound scattering, and, for example, air bubbles are extremely effective sound attenuators. High viscosity at low temperatures increases US attenuation [28]. A similar observation was that the effect of US on the mass flow decreased as the viscosity increased, but US still had an effect on the mass flow at 50 °C. It may be that US treatment had an effect mainly on the surface properties of extrudate due to the rapid attenuation in the viscous supercooled melt.

3.2.1. Problems in ultrasound-assisted extrusion

The extrudate was easy to collect on the moving paper or other moving surface that can be connected to the cutting device. Piston movement should be constant to achieve constant extrudate flow from the nozzle onto moving paper. Thus, pressurized air is not an ideal setting for moving the piston because of the possible physical in-homogeneity of the sample.

The main problem in achieving good extrudate is the air bubbles in the extrudate. During pre-melting, a temperature probe was set in the sample tank, and the sample was gently mixed with a glass rod to achieve a homogenous mass. Mass mixing entrapped air bubbles inside the mass. Oscillating air bubbles broke down the extrudates in the US nozzle. The number of pieces cut approximated that of the bubbles in the extrudate/sample tank. The cutting of the extrudate was more efficient when the higher US power was used in the nozzle (Fig. 7b). In future experiments, a vacuum should be used in the sample tank during pre-melting to decrease the amount of bubbles in the sample. In the preliminary tests, it was observed that ultrasound could also be used to remove the bubbles from the sample tank. However, the removal of bubbles will need further development of the equipment presented, but it is possible as shown in the literature [29].

3.3. Cutting tests

In our study, US-assisted cutting was observed to be more effective than cutting without a US-assisted knife. The material stuck to the blade surface at all cutting temperatures. At 25 °C, the extrudate was destroyed when cutting was attempted with or without US. The extrudate broke down into smaller pieces with US than without US. Extrudate was too fragile to be cut with US at 25 °C. The extrudates cut with a US blade are presented in Fig. 8. Cutting temperatures between 40 and 50 °C may be ideal for this system. At 60 °C, extrudate cuts melted around the corners. Slight melting was also observed when the cut was made at 50 °C. At 40 °C, the edges of the cuts were sharp and not rounded due to melting. No difference was detected in the appearance of the cuts when different US power levels were used (50 or 100 W). The weight of a 5 mm extrudate cut was approximately 12–13 mg. In the preliminary tests, the string cutter was tested only with in-line cutting and it worked well. The material of the string is the most critical factor because it is exposed to high mechanical stress due to US. Due to the mechanical stress of the US vibration, the string may snap easily during processing because of the small cracks in the metal of the string. The US-assisted knife is more durable under mechanical stress because of its bigger size.

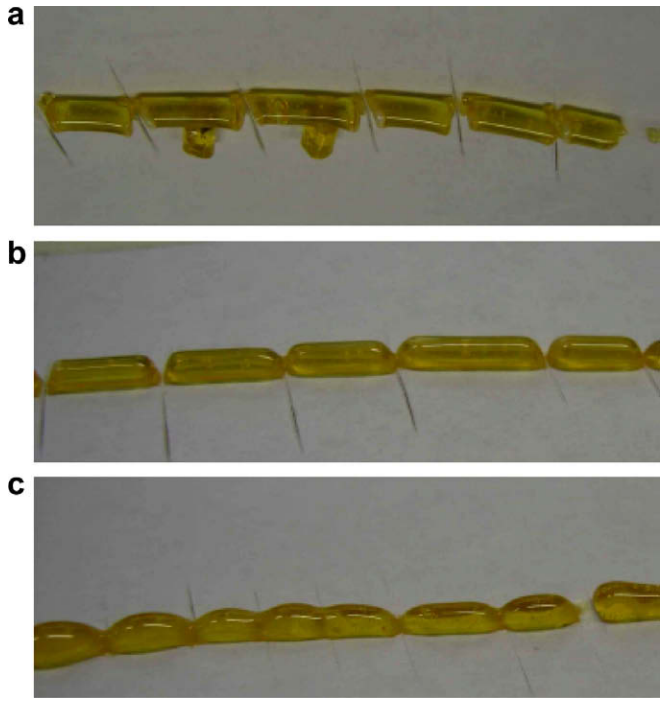

Fig. 8. Extrudates cut using an ultrasound knife with a power of 50 W at different temperatures (a) 40 °C, (b) 50 °C, (c) 60 °C.

Sticking to the blade decreased markedly with US. Also, many other benefits explain why US cutting has replaced traditional cutting devices in the food industry [30]. In food cutting, the frequency is usually set between 20 and 50 kHz. In this study, a frequency of approximately 20 kHz was also observed to be effective for cutting amorphous sticky material. The vibrating metal surface might be one reason why US decreases stickiness, because the material does not have enough time to make contact with the vibrating metal surface. It has also been found that the cracks on the metal surfaces trap air bubbles that start to cavitate when US is used [31], and this might decrease the stickiness owing to poor contact between the metal and sample. US cutting has been proposed for creating new products that were impossible to cut with traditional cutting blades [30]. One problem, however, in US cutting might be the heat formed during the process. At cutting, the surface temperatures can be as high as 200 °C. However, the surface temperature of the material is proportional to the US power used and the contact time [32]. Temperature increase during cutting may trigger crystallisation of amorphous sample or may induce chemical degradation. These properties are discussed in the article Hoppu et al. [33]. Since normal material cutting lasts milliseconds, heat formation should not be a problem. Blade or extrudate warm-up was not observed to be a problem in this study due to the short cutting time. However, it is still important to have a cooling system to decrease the heat generated by the mechanical friction between the blade and extrudate. Acoustic cavitation during cutting is also reported to change olfactory properties of foods [34], but cavitation is unusual in viscous material.

4. Conclusions

Melt-quenched citric acid and paracetamol or blends with 25%, 50%, and 75% (wt%) paracetamol were studied using a constructed stickiness and resistance to deformation compartment. The 50/50 blend was chosen for the ultrasound extrusion and cutting study. This 50/50 blend has been observed to be physically stable for years when stored in dry conditions at 25 °C [10,15].

The present study confirmed that stickiness and resistance to deformation are related to viscosity and glass transition temperature. The 50/50 blend was observed to be a sticky model material at ambient temperature. Using our measurement method the stickiness was highest at T_g + 10–15 °C as presented, e.g. for sugars in the earlier reports. Although the material was sticky, it could be processed by ultrasound-assisted cutting and extrusion.

Sample flow through the ultrasound nozzle increased with the increase in ultrasound power. A higher experiment temperature increased the mass flow through the nozzle as expected due to the decreased viscosity. The problem in ultrasound extrusion was the bubbles entrapped into the material during the sample preparation. These bubbles started to cavitate when the ultrasound power was switched on and the cavitation broke down the extrudates and mass flow was not continuous. However, in future studies the ultrasound nozzle is directly installed into the screw-extruder, which should decrease the bubbles formed during the sample preparation.

The 50/50 blend did not stick to the blade when the ultrasound blade was used, whereas the sample stuck to the blade without ultrasound. The ultrasound blade has a self-cleaning property. In addition, extrudate cuts were more disk-shaped without squashed edges compared with the samples cut without ultrasound. The optimal cutting temperature was estimated to be between 40 and 50 °C for our 50/50 blend, which is approximately 25–35 °C higher than the glass transition temperature. A detailed study of the influence of ultrasound on the physical stability of extrudated and cut material is presented elsewhere [33].

Acknowledgments

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