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Micro-mechanical properties of drying material bridges of pharmaceutical excipients

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Abstract

This work is part of a larger research effort to elucidate the properties and morphology of pharmaceutical granules produced by wet-granulation. In this work, we measure forces exerted by the drying interparticle bridges. The bridges were formed from aqueous solutions of common pharmaceutical excipients both non-polymeric (lactose, mannitol) and polymeric (hydroxypropyl cellulose (HPC), hydroxypropyl methylcellulose (HPMC), polyvinylpyrrolidone (povidone) (PVP)). We also study the morphology, microstructure and crystalline structure of solidifying bridges. We find that the solidifying behavior and final properties of bridges differ dramatically, depending on the composition of the solution. Bridges containing only lactose or mannitol tend to expand upon solidification, pushing the ends of the bridge apart; in contrast, pure HPC, HPMC, or PVP bridges tend to contract. Bridges crystallized from solution of the pure non-polymeric excipients are polycrystalline, brittle, and have low strength; bridges from the polymeric excipients are amorphous, strong and tough. When the polymeric and non-polymeric excipients are used together, behavior closer to either one or the other extreme takes place. This depends on the relative amount of polymer in the bridge. It was also found that the different polymers impart different behavior on the bridge. The observed differences in solidification behavior have important implications for granule formation, drying and ultimate bridge and granule properties; these are discussed at some length in the paper.

Keywords: Granulation; Granules; Lactose; Mannitol; HPC; Binders

1. Introduction

In a previous paper (Farber et al., 2003b), we studied the evolution of drying material bridges of pharmaceutical excipients. We looked at the structure and morphology of drying bridges as a function of time as solvent (water) evaporated from a concentrated solution of lactose and mannitol. Sub-millimeter size bridges were

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formed on and between microscope slides and their evolution was observed directly under magnification. The study was supplemented with X-ray diffraction measurements and conclusions were drawn with specific application to granulation of fine powders and tabletting. We found that solid bridges formed from these concentrated (saturated) solutions of pharmaceutical non-polymeric excipients in several stages and the material undergoes structural changes from a mostly amorphous state to a characteristic crystalline structure. The time required for the completion of these stages was found to be quite long, of the order of hours and sometimes even days so that the final bridge microstructure was not obtained immediately. The significance of these results to the formation and final properties of tablets made from the dry granules was also studied in detail.

The above work is part of a more extended program to elucidate the formation of dry granules from wet, so-called "green" agglomerates made of a dry powder mix and a solvent (water or ethanol) containing binder (usually a polymeric excipient such as HPC, HPMC and PVP) and some of the original powder in a saturated solution (Bika et al., 2005). Measurement of the strength and morphology of the dry granules obtained from granulation of non-polymeric excipients such as lactose and mannitol showed that these granules exhibit very complex structures. The complexity stems from the way the original small powder particles are connected to each other inside the granule. X-ray tomographic studies (Farber et al., 2003a) of dry agglomerates also showed the complexity of the structure and gave details of how stresses in the wet phase of agglomeration influence the final internal morphology of the granules. Together, the above detailed studies showed the extremely complex nature of wet granule formation and subsequent drying and crystallization to obtain final dry granule with well-defined properties. The most important micro-level entity inside the granule that most directly determines its properties proved to be the solidifying excipient-saturated bridges that ultimately influence the final outcome.

We expand the above study in this paper by measuring forces exerted by the solidifying bridge on two stationary surfaces between which the bridge is formed. We follow the evolution of the forces in time as solvent evaporates and material solidifies and crystallizes to form the dry micro-bridge with a well-defined strength. The implication of these results in granulation, grinding and tabletting of pharmaceutical ingredients is highlighted. To simplify nomenclature, we use in the text below the designation "excipient" for all non-polymeric pharmaceutical powders such as lactose and mannitol and we use the designation "polymers" or "polymeric binders" for all polymeric excipients such as hydroxypropyl cellulose, hydroxypropyl methylcellulose, polyvinylpyrrolidone (povidone) (HPC, HPMC and PVP, respectively).

2. Experimental

2.1. Apparatus

The experimental set-up used during the present measurements is shown schematically in Fig. 1. It is composed of a computer controlled uniaxial mechanical testing instrument (TA-XT2i Texture Analyzer, Stable Micro Systems, Surrey, England) equipped with very sensitive force and motion transducers mounted to the upper fulcrum of the instrument and a fixed lower fulcrum that forms the base of the instrument. Two transparent glass slides were mounted (fixed) on the fulcrums as shown in the figure and the liquid bridge was formed between them. An Olympus SZX 12 stereo microscope equipped with the Spot digital camera was positioned so that the drying bridge was always in its view with illumination from either below (as long as the bridge was transparent) or from the side. The whole instrument was contained in a climate-controlled enclosure (not shown in the figure) in which both the temperature and the relative humidity (RH) could be controlled very precisely and changed at will as a function of time. The relative humidity in the box ranged between 20 and 60% RH. The majority of tests were performed at 20% RH and 38 °C; these were considered typical of drying conditions of pharmaceutical granules. Some select experiments were also carried out at room temperature. If not specifically mentioned in the text, the results discussed were performed at a temperature of 38 °C.

Two kinds of measurements were performed. In the first kind of test, the bridge was formed by stretching a droplet of test solution of known initial volume between the glass slides. During the test, the length of the bridge was held constant, and the total force

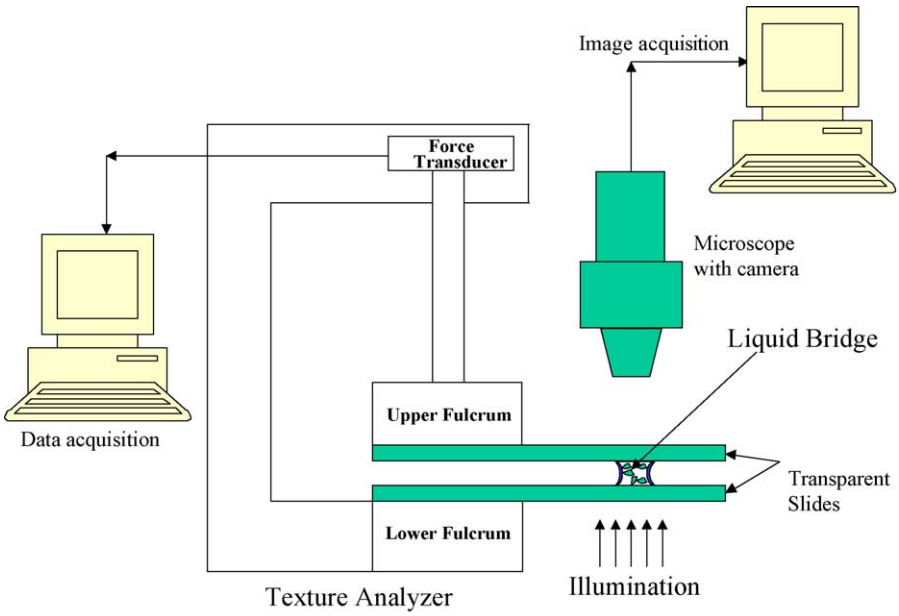

Fig. 1. Schematic of the instrument used to study solidifying bridges.

on the fulcrums was recorded as a function of time at the prevailing conditions of temperature and relative humidity. Upon complete drying and crystallization (this was determined from the measured strength of the bridge when it ceased to change in time) the experiment was either terminated or a new set of temperature-and-relative-humidity were imposed until steady state was again achieved. In the second set of tests, the dry bridge strength was determined by applying additional external force and following its deformation and ultimate rupture.

2.2. X-ray powder diffraction

Powder X-ray diffraction (PXRD) measurements were made with a Bruker-Siemens D5000 using Cu Kα radiation (tube operated at 40 kV/40 mA). The hardware included a parallel beam mirror, 1 and 0.6 mm diverging beam splitters and a graphite monochromator. Data was collected in a 2θ range from 5° to 45° under lock-coupled scan mode with a step size of 0.02° and a step time of 4 s. The powder sample was lightly packed into the standard sample holder and the top surface was smoothed using a glass microscope slide. For X-ray analysis of bridges, they were separated from the supporting glass slides under the optical microscope using sharp scalpel. Areas adjacent to the glass were carefully separated and excluded from analysis unless otherwise mentioned.

2.3. Materials and experimental conditions

Solutions to form wet bridges were prepared using corresponding amounts of powder (pharmaceutical excipients, such as lactose and mannitol and polymeric binders, such as HPC) and HPLC grade water. Materials used in this study are listed in Table 1. The composition and the amount of different materials in each solution are shown in Table 2. In the figures and tables presented here, the sample name reflects its

Table 1
Materials used in this study

Material	Grade	Manufacturer
Mannitol	Pearlitol SD 200	Roquette
Lactose	Anhydrous	Quest Int.
HPC	EXF	Klucel
HPMC	2910 (606 Pharmacoat)	Shin-Etsu Chemicals Co., Ltd.
PVP (povidone)	K-29/32	BASF

Table 2
Composition of aqueous solutions used in the study (wt%)

System	Pure excipient[a]	Composition I	Composition II	Pure binder
Mannitol-based	15% M[b]	15% M–5% HPC	5% M–5% HPC	10% HPC
	18% L	18% L–5% HPC	5% L–5% HPC	10% HPC
Lactose-based			5% L–5% HPMC	10% HPMC
			5% L–5% PVP	10% PVP

M, mannitol; L, lactose.
[a] At saturation at 20 °C (mannitol) and 25 °C (lactose) Handbook of Pharmaceutical Excipients (1986).
[b] In figures, sample name reflects its composition by the following way: 15% mannitol is denoted as M15; 15% lactose–5% HPC is denoted as L15–HPC5, etc.

composition in the following manner: 15% mannitol is denoted as M15; 15% lactose–5% HPC is denoted as L15–HPC5, and so on. Powder to water ratios in some mannitol- and lactose-containing solutions were selected as 1:5.6 and 1:4.6, respectively, i.e. at the saturation limits for these excipients at 22 °C (Handbook of Pharmaceutical Excipients (1986)). Other combinations of concentrations were also used as shown in Table 2.

To form a liquid bridge, a 5 μl droplet of a solution prepared as described above was placed on the lower glass slide (as shown in Fig. 1) using a calibrated micropipette. Subsequently, the upper arm of the Texture Analyzer was lowered until the droplet contacted the glass on the upper arm forming a bridge that was then stretched to typically 0.7 mm distance. The force developed in the system was then monitored as a function of drying time as described previously. To minimize the influence of the glass slide on the properties of the bridge, the slides were carefully washed with de-ionized water and surfactant, rinsed and dried thoroughly before use. To make the adherence of the liquid bridge to the glass as flawless as possible, we used the rough side of the slide to produce the bridge. Even with these precautions, some bridges detached from the glass surface upon stretching; this mostly happened at higher relative air humilities and more often with the PVP polymer compared to the other used during experimentation. The majority of bridges, however, failed in the middle section of the bridge, which suggests that the glass–bridge interface did not play any significant role in bridge failure. Unless otherwise mentioned, the results reported in the paper are for the bridges that did not separate during tests.

3. Experimental results

3.1. Solidification

A typical time evolution of forces that develop during solidification is shown in Fig. 2 along with images of a drying bridge recorded “in situ”. As seen in Fig. 2a, following an initial relatively short “induction” period, significant tension force (of about 47 g) developed in the system as seen in the lower part of Fig. 2a, which is an expanded view of the upper graph at short times. Subsequently, the overall force exerted on the fulcrums decreased slightly and then leveled off after approximately 2000 min.

Microscopy performed while the force was measured reveals that the short induction period corresponds to shrinkage of the liquid bridge as seen in Fig. 2b. Significant force develops in the system only after the bridge shrinks and becomes stationary after about 25 min. Following this last stage, microscopy did not reveal any further changes in overall bridge volume or shape even though the tension in the bridge changes dramatically.

As seen in Fig. 2b, the initial liquid bridge was continuous and cylindrical in shape: the black circle in the figure shows the limit of the liquid bridge and its curvature as it spreads on the glass slide. As water evaporates, the bridge shrinks, and two distinct bridge shapes were observed to develop depending on the composition of the initial solution. For some solutions, the bridge retained its overall cylindrical shape (such as that shown at 15 min in Fig. 2b) while for other, the complex geometry (with a cross-section resembling a horseshoe) depicted in Fig. 2b developed during the initial stages of drying. All these transformations occur

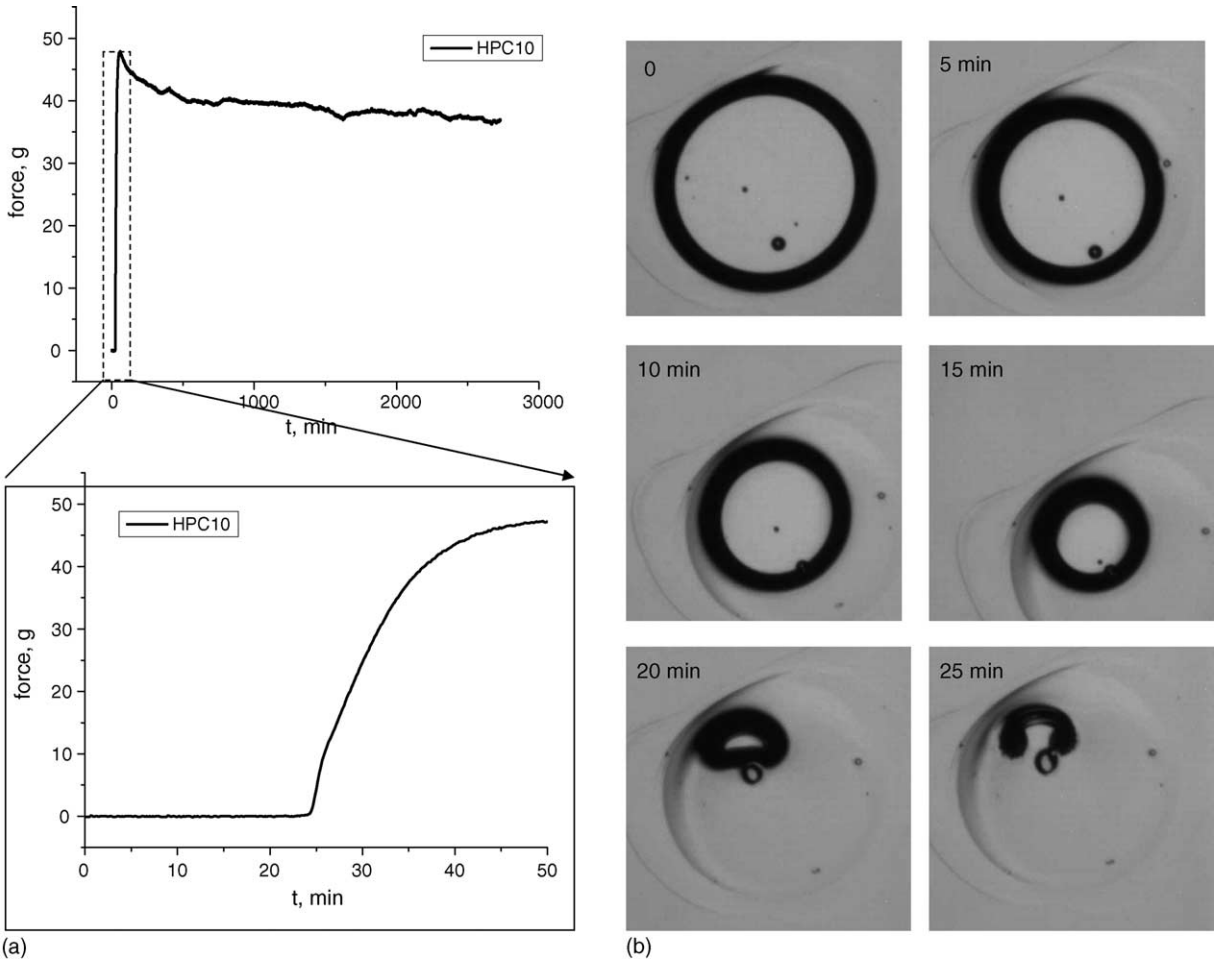

Fig. 2. (a) Typical time evolution of stresses developed during solidification of a bridge (10% HPC solution, denoted here as HPC10) and (b) typical geometry evolution of a drying bridge at the initial stages of drying (time evolution of stresses for this bridge is shown in (a)).

prior to the development of any significant stresses in the system as mentioned above.

3.2. Effect of concentration

The evolution of forces as a function of time is shown in Fig. 3a and b for drying bridges at 38 °C containing various amounts of excipient and binder for the mannitol–HPC and lactose–HPC systems, respectively. In bridges formed from pure lactose or mannitol (denoted in the legends as "L" and "M") significant stress developed as a result of solidification/crystallization, and as seen, the bridge exerted a negative force on the fulcrums of the testing machine. This implies dilatation of the bridge during drying. The bridge itself is under compression. At the opposite extreme when there is no excipient present and only the effect of pure HPC is measured (curves denoted as "HPC" in the legend), significant positive force develops, indicating contraction of the bridge during drying. As a result, the bridge itself is under tension. Bridges formed from a 5% HPC–5% mannitol or 5% HPC–5% lactose solution exert forces during solidification similar to the pure HPC bridges, although their magnitude was smaller than that of the pure HPC bridge. In a bridge made of 16% mannitol or 18% lactose (excip-

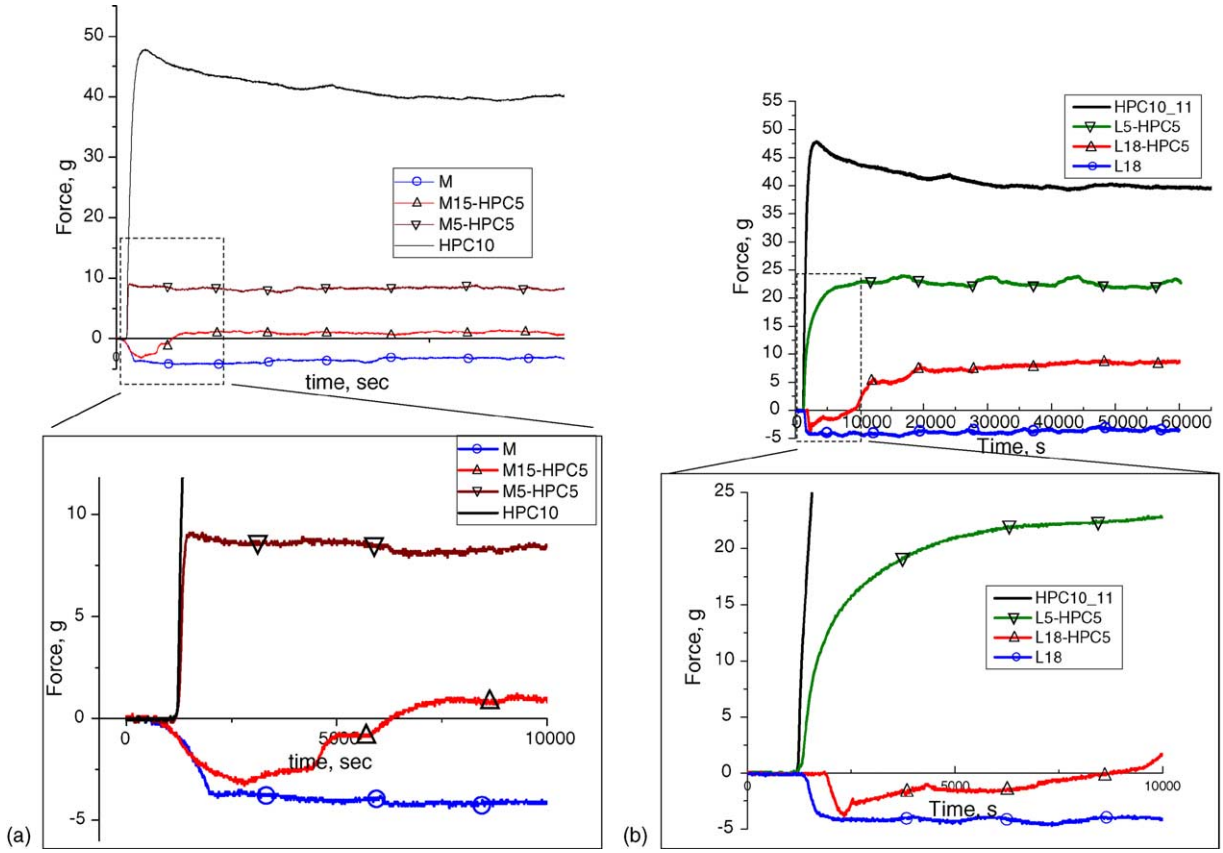

Fig. 3. Evolution of stresses during solidification as a function of time: (a) mannitol–HPC system; (b) lactose–HPC system; (c) lactose–HPC system (at room temperature).

ient close to the saturation level at room temperature) with 5% HPC, dilatation of the bridge occurs at the beginning, but then a contraction takes over as in the case of the pure HPC bridge. Thus, the material in the bridge came under an internal tension stress after solidification, similar to the bridge made of 5% manitol–5% HPC.

3.3. Effect of temperature

Results of bridge solidification at room temperature were qualitatively similar to the results at higher temperature as described above. Fig. 3c shows solidification curves for the HPC–lactose system at room temperature. As seen, drying times were significantly longer than at 38 °C, but the overall behavior was similar in that pure excipient bridges tended to dilate while bridges with increasing HPC content tended to contract, with tensile stresses increasing with increasing polymer concentration.

3.4. Mechanical properties

The response of the dry bridges to uniaxial tension is shown in Fig. 4a and b for mannitol–HPC and lactose–HPC bridges, respectively. During these experiments the *dry bridge* was subjected to uniaxial tension until it either ruptured or separated from the glass slide. Rupture occurred either at the contact of the bridge with the glass slide or in the middle of the bridge; both scenarios were present and notice is given in each case as to the point of rupture.

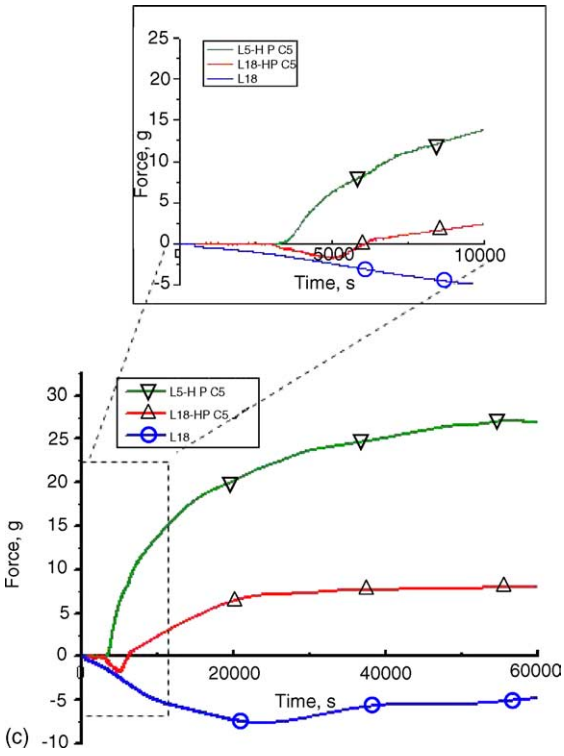

Fig. 3. (*Continued*).

Pure mannitol bridges were not able to sustain any significant amount of tension and broke close to the bridge–glass interface. Mannitol bridges containing HPC on the other hand, were able to sustain significant amount of tension force. As seen in Fig. 4a, at lower force levels, the response is quasi-elastic but the material started to yield at higher forces.

Unlike pure mannitol, pure lactose bridges were able to sustain significant amount of tension. They often separated from one of the glass slides during the tension experiment, otherwise remaining intact. In the remaining cases, they broke close to the bridge–glass interface. Lactose bridges containing HPC failed after yielding in a similar way as mannitol bridges containing HPC.

Pure HPC bridges had very high strength at breaking as seen in the figure, and they failed after significant yielding. In all these results, the beneficial influence of the polymer is apparent, even in the case of the lactose bridge that had relatively high yield strength by itself. The presence of the polymer in all cases made

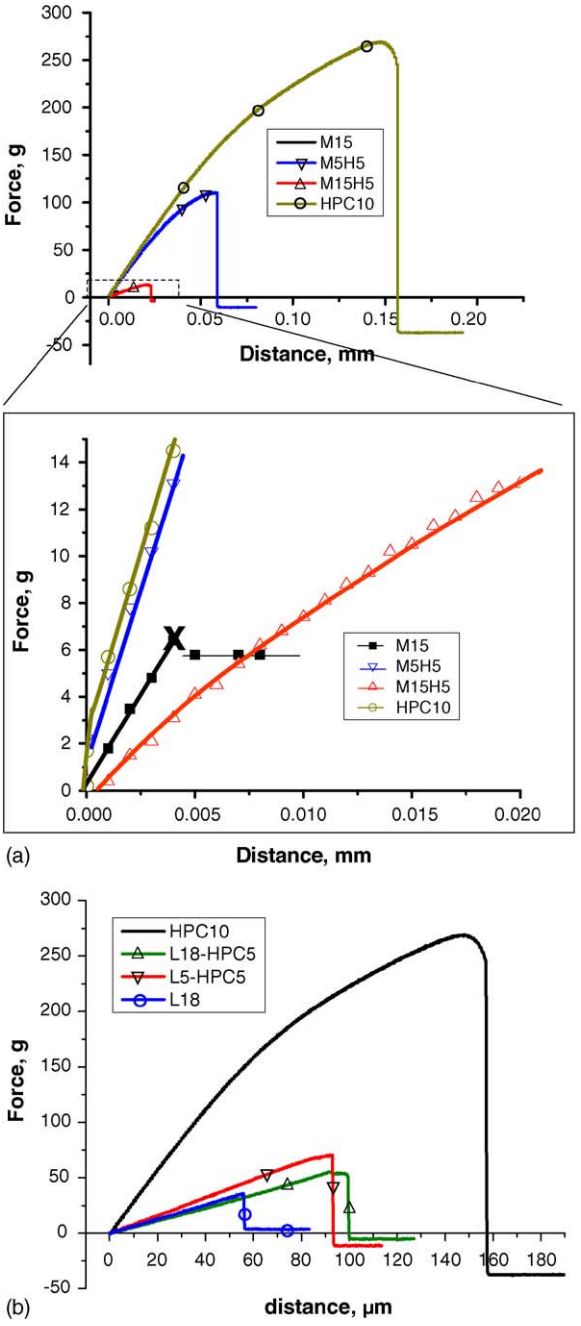

Fig. 4. Response to uniaxial tension of the dry bridges in: (a) mannitol–HPC system and (b) lactose–HPC system.

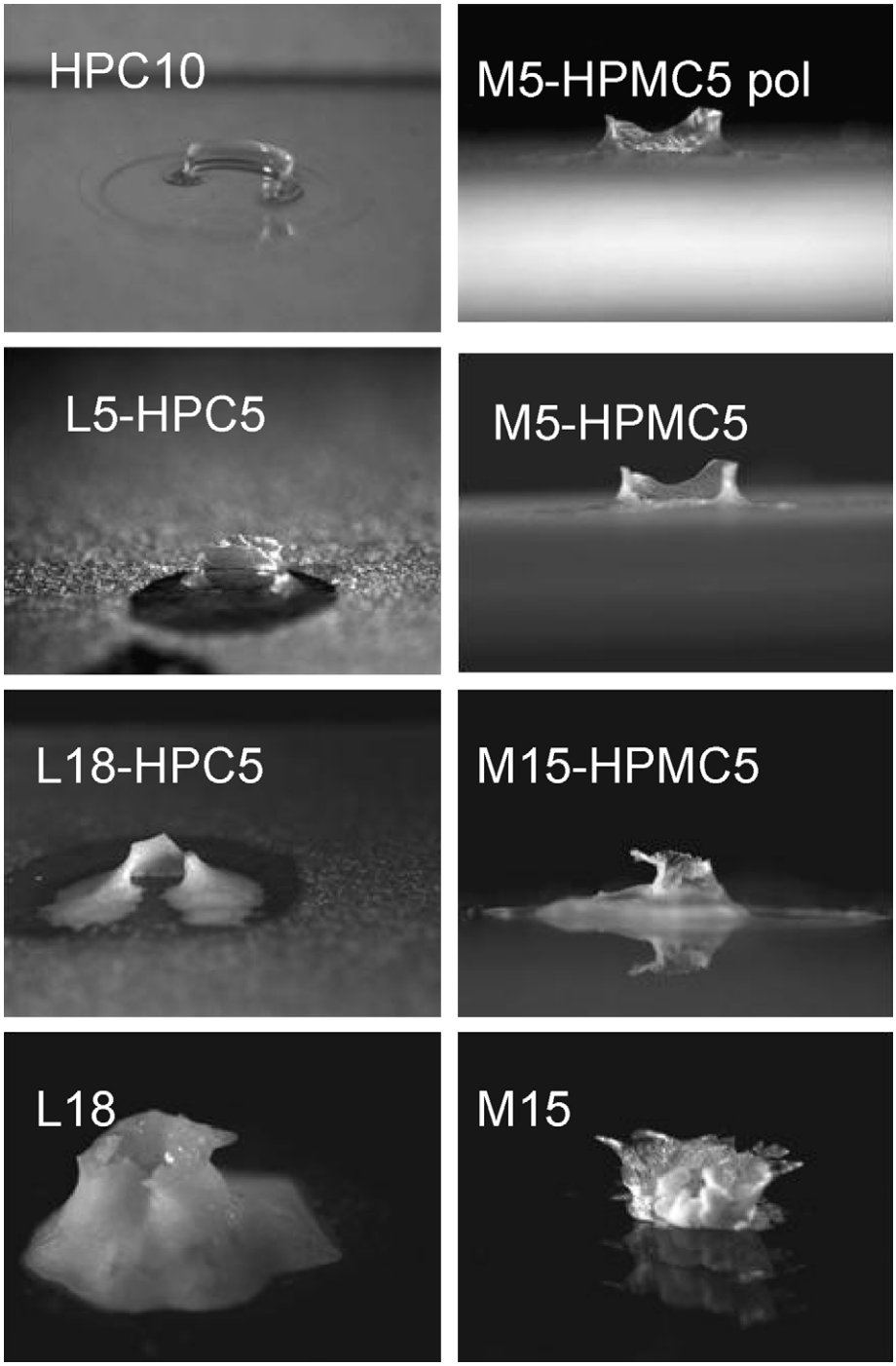

Fig. 5. Optical micrographs of bridges after failure in the tension experiment (pol., polarized light).

the bridges more malleable hence being more resistant to breakage.

3.5. Morphology and phase composition

Representative images of bridges after failure in the tension experiment are shown in Fig. 5. The pure HPC and 5% HPC–5% excipient bridges were transparent under illumination with non-polarized light. Microscopy with polarized light did not reveal any crystals in the pure HPC and 5% HPC–5% lactose bridges, whereas very fine and well-aligned needle-like crystals were present in the 5% HPC–5% mannitol bridge. Bridges consisting of pure mannitol contained much coarser elongated crystals that were easily observed in conventional light. Pure lactose bridges on the other hand, appeared to consist of very fine crystals.

Microscopy also revealed that failure in pure HPC- and HPC-containing bridges propagated in the middle section of the bridge approximately normal to the axis of applied tension. Pure mannitol on the other hand failed close to the glass interface where the crystals were especially large. As mentioned earlier, pure lactose bridges typically also failed close to the glass interface or separated from the glass.

An XRD pattern of the material in the solidified HPC–mannitol bridge is shown in Fig. 6 along with the pattern of the starting material. Although the initial solution was prepared using β-mannitol, the bridge-material that formed in the mannitol–HPC system, was δ-mannitol, consistent with observations in our earlier work (Farber et al., 2003b). The presence of needle-like crystals in the film agrees with previously reported crystal-shapes of δ-mannitol. For solidified crystalline lactose–HPC bridges, the XRD spectrum contains reflections of the anhydrous β-lactose, in addition to the presence of the original lactose monohydrate.

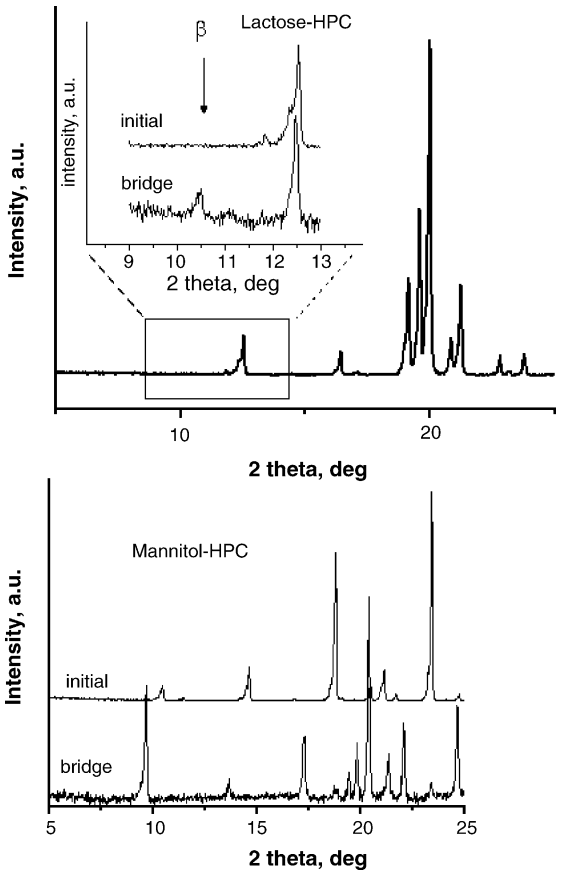

Fig. 6. XRD patterns of the material in the solidified bridges.

3.6. Effect of relative humidity

The effect of relative humidity on bridge solidification was studied for the 5% HPC–5% lactose bridges, and the results are shown in Fig. 7a and b. Fig. 7a shows the force developed during drying to a total time of about 10,000 min while Fig. 7b shows the deformation and rupture of the dry bridge under tension. As seen in Fig. 7a, the force that develops at higher humidity is smaller than that developed at lower humidity. Additionally, the induction period is longer at higher humidity.

When these same bridges were subjected to tension and rupture (see Fig. 7b), their properties were also significantly affected by humidity during the experiment. At low relative humidity of 20 and 30% RH, the bridges deformed elastically until they failed in brittle fashion. At 40% RH, on the other hand, the bridges yielded at a significantly lower force. At some point during yielding, they typically started to separate from the glass substrate without rupture. We conclude from these results that deformation to failure is much higher at 40% than at 20 and 30% RH, and that a brittle-to-ductile transition exists between 30 and 40% RH in

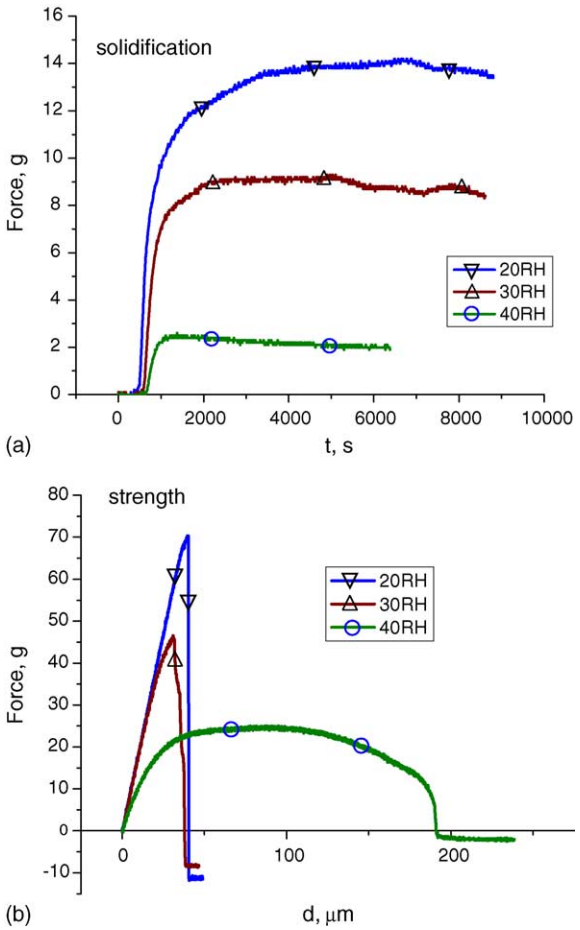

Fig. 7. Effect of relative humidity on bridge strength during: (a) solidification and (b) tension experiment.

the material. This is consistent with the glass transition temperature in this material being a function of the relative humidity.

3.7. Nature of the binder polymer

We found that different polymers used as binders affect differently both the kinetics of stress development and the final properties and microstructure of the formed bridge. To better understand the kinetics and magnitude of stress development in bridges containing excipients and binders, bridges of *pure binder solutions* were tested first. The measurements included PVP, HPMC and HPC and typical solidification curves are shown in Fig. 8a (the lower part is an expanded detail of the upper stress response at very short times). As seen, all bridges developed a tensile stress within 10–15 min. PVP developed the highest stress, but the bridge failed abruptly in brittle mode after about an hour. Although HPC and HPMC bridges developed significantly lower stresses, they remained intact.

We should also note the features of stress development for the above cases (see lower graph in Fig. 8a): the stress started to increase rapidly in all bridges. In the HPC bridge, this increase was monotonic. In the PVP bridge, the stress decreased suddenly at about 1000 min but then quickly increased again. In the HPMC bridge, two of these stress decreases were registered between 750 and 1000 min. Such behavior was also observed in previous work (Tardos and Gupta, 1996) where polyethylene glycol (PEG) bridges were stretched between two 5 mm diameter glass spheres and the overall force was measured. These bridges showed multiple internal ruptures during drying but eventually also maintained a relatively large pulling force at steady state. We assume that in the present experiments, the local drop in stress levels signifies an internal polymer-ligament rupture that results in the release of some internal stress in the bridge. An alternative explanation may be that some semi-crystalline polymers (the kind that actually form these bridges) can show multiple yield points due to the mixed physical states (amorphous and crystalline) or partial brittle fracture from the glassy regions and yield behavior from the ductile regions.

The effect of the nature of the binder on solidification of bridges containing 5% lactose and 5% of the three different polymers PVP, HPC and HPMC is shown in Fig. 8b. All three binder-containing bridges resulted in the development of tensile stresses. However, the magnitude of the stress and the kinetics of their development differ significantly. PVP-containing bridges developed the highest stress, however this required several days to become constant. Bridges containing HPMC and HPC developed stress within minutes; a typical time for HPMC-containing bridge was about 10 min versus about 15 min for HPC-containing bridge. HPMC-containing bridges developed a somewhat higher stress than HPC and relaxed slightly to a constant value after about an hour. However, if the length of the HPMC bridge (distance between glass

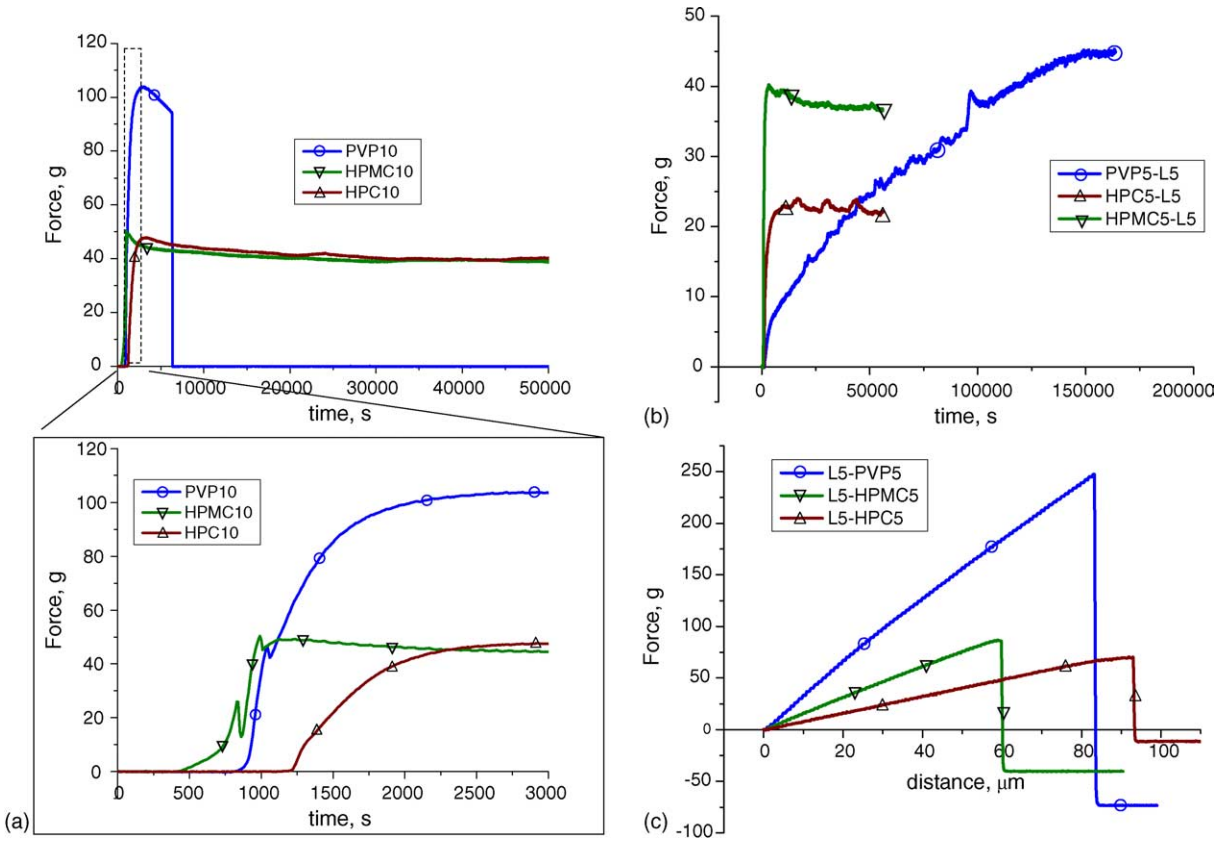

Fig. 8. Effect of the nature of binder on solidification of bridges and response in the tension experiment: (a) solidification—different pure binders; (b) solidification—5% lactose–5% binders; (c) tension experiment—5% lactose–5% binders; (d) optical micrographs of bridges after failure in the tension experiment.

slides) was larger than the typical 0.65–0.7 mm during liquid bridge formation, the stress level in the bridge was significantly smaller, sometimes up to an order of magnitude, and the bridge typically broke within minutes after the stress had leveled off. In contrast, long HPC bridges developed lower stress but remained intact as they dried.

The response of dry bridges to uniaxial tension is shown in Fig. 8c for bridges containing 5% lactose and 5% of different binders. The PVP-containing bridge proved to be much stronger than the HPC- and HPMC-containing bridges. All bridges appeared to fail in brittle fashion. Closer examination revealed that the PVP-containing bridge failed in completely brittle fashion while the HPC- and HPMC-containing bridges failed after some minor yielding; this was more pronounced in the HPC-containing bridge.

Representative images of bridges after failure in the tension experiment are shown in Fig. 8d. Bridges of pure binders were similar: they were all film-like, transparent and assumed a horseshoe shape in their cross-section. Addition of lactose to the HPC and HPMC solutions did not affect the shape and morphology of the bridges. Bridge solidification of lactose-PVP solution, on the other hand, yielded a columnar-like bridge. This morphology change indicates differences in the interaction of PVP with lactose as compared to HPC and HPMC.

We were unable to evaluate the mechanical properties of *pure* HPMC and PVP bridges using the method of two glass slides because HPMC bridges typically separated from the glass substrate after some stress, whereas PVP bridges self-ruptured during stress development.

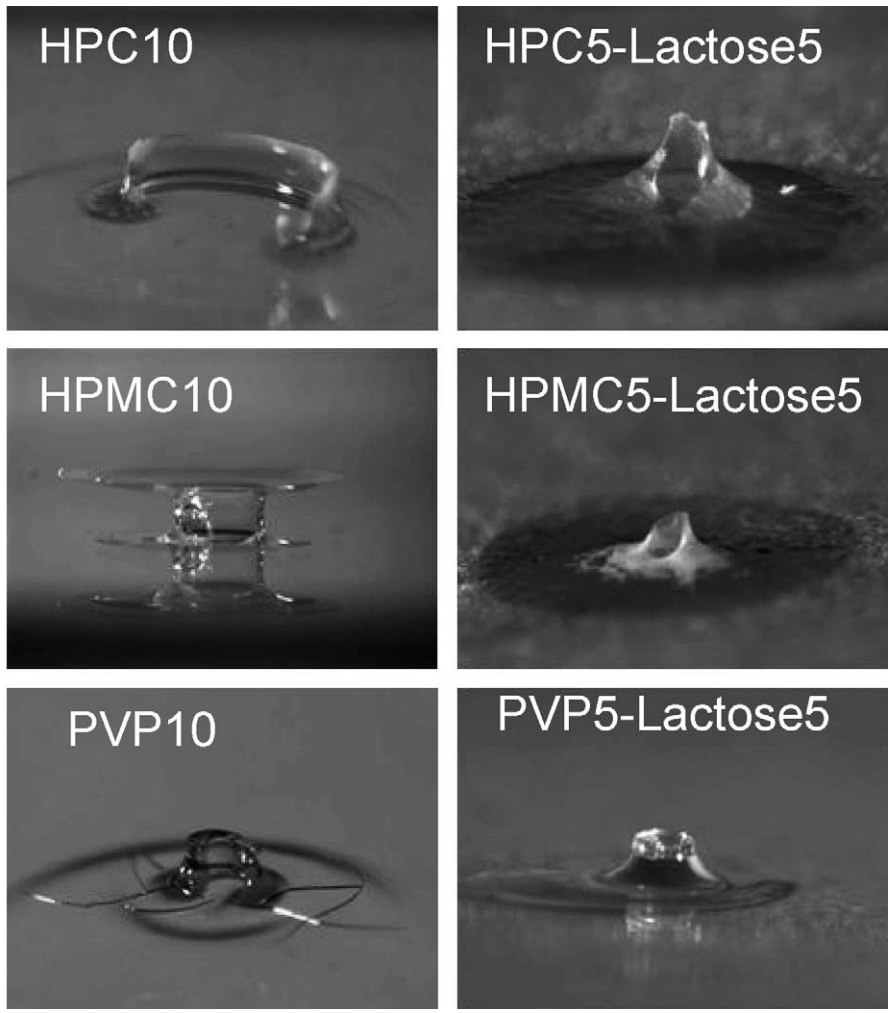

Fig. 8. (*Continued*).

4. Discussion

The results of this study demonstrate that the presence of polymers in the solution has a dramatic effect on the stress state, mechanical properties and morphology of solidified bridges that form from the solutions. We also found that significant internal stresses can develop in these bridges.

Bridges solidified from solutions of pure lactose or mannitol are polycrystalline and brittle. Thus, it is not surprising that these bridges were not strong and not able to sustain any significant external tension stress. This explains the fact that dry granules, made from pure lactose or mannitol and using pure water as a binder, are weak. This is not because solid bridges are not forming or there is not enough solid material in the bridges, it is simply because these bridges are inherently weak and develop internal stresses that are compressive or in other words tend to push the granule apart.

In contrast, a bridge solidified from a pure solution of a typical polymeric binder such as HPC is non-crystalline. It is very strong and tough. As a result, it can sustain very high external tension stresses without failure and it fails after significant yielding. This explains why when HPC aqueous solutions are used as

a liquid binder for non-soluble material, such binders usually provide excellent dry granule strength.

Addition of HPC to a soluble excipient changes the mechanical properties of the bridge material dramatically. Under the conditions of the present experiments, about 5% of polymer in saturated solutions of the above excipients was enough to provide an adequate combination of strength and toughness. This kind of modifying behavior is widely exploited in industry where it is well known that a certain well-determined amount of "binder" or polymer is required to produce granules with desirable milling and compaction behavior.

We also found that significant internal stresses can develop in bridges during solidification. Bridges of pure excipients dilate as they dry and crystallize, which results in exertion of "pushing" forces on the fulcrums of the testing machine, bringing the formed bridge under compression. Just the opposite occurs with pure polymer bridges: polymer bridges contract during solidification, which brings them under tension. The development of these stresses is notable, as they potentially can act as a driving force for granule consolidation that occurs as green granules are agitated and dried, for example during fluid-bed granulating or drying. In addition, the bridges are likely to retain these stresses after they are dried, which may affect dry granule strength and related properties such as attrition resistance and compactability. For dry bridges that deform plastically, these residual stresses will relax at a rate that is dependent on composition, temperature, and moisture content (i.e. relative humidity). Thus, the development of tensile or compressive stress in drying interparticle bridges could be responsible for time-dependence that is sometimes observed in the milling and compaction behavior of wet-granulated powders.

As this study clearly reveals, solidification behavior of bridges made from a solution of HPC and mannitol or lactose may be rationalized as a combination of the two opposite behaviors described above. The net result should depend on the mannitol-to-HPC-ratio in the liquid. Indeed, when the HPC share is high enough, the behavior and properties of the bridge is HPC-like starting from the initiation of stress development during solidification, as in 5%/5% bridges. When the amount of mannitol is significantly higher than that of HPC, as in the 5%/18% solution, mannitol-like behavior develops initially. As the bridge develops in time however, HPC-like behavior prevails. Apparently, with an even higher share of mannitol, the net behavior should become totally mannitol like. Thus, under the conditions of the present experiments, about 5% of polymer in saturated solutions of the above excipients was enough to eliminate polymeric binder-like behavior.

The stress development and properties of mannitol–HPC like bridges can also be rationalized in terms of microstructure formation. Typically, crystallization from pure mannitol/lactose solutions starts at one or several locations on the liquid–substrate interface, i.e. at the foot of the bridge, and crystals grow from these locations towards the center of the bridge (Farber et al., 2003a,b). It can be expected that significant force starts to develop in such bridges only when the growing crystal regions meet, interlock and start to interact from top to bottom of the bridge. Apparently, further crystallization results in expansion of crystalline regions and development of the "pushing" behavior. Similar behavior was reported previously for bridges crystallized from sodium chloride solutions (Tardos and Gupta, 1996). Unlike crystalline lactose and mannitol, solidifying HPC films remain amorphous and shrink as they dry. Apparently, early on, stresses are relaxed by rearrangement of polymer molecules and/or their relaxation. As the water content decreases, the polymer rearrangement becomes too slow while relaxation time becomes too long, and tensile stresses develop.

Mannitol and HPC are mutually miscible in water but apparently not able to form extensive solid solutions in each other. Water removal from mannitol–HPC solution will lead to crystallization of the sugar and enrichment of the remaining surrounding regions of the solidifying bridge with HPC. As a result, any bridge formed from the mannitol–HPC solution will consist of amorphous HPC-rich film and mannitol crystals. The overall properties then will be controlled by the microstructure that develops during crystallization. Interlocking of crystals from top to bottom will lead to the "pushing" behavior, while formation and drying of a continuous HPC matrix should result in "pulling". Apparently, when enough HPC is present, such an HPC matrix forms.

Our study also demonstrates that there is a significant difference in interaction of different polymers

with major excipients. All polymeric binders used in this study provided "binding" capabilities at solidification, i.e. changed the stress state of the solidified bridge from internal compression (if no binder added), to tension. However, both the kinetics of stress development and the shape of the bridge differ. HPMC- and HPC-containing bridges were close in both solidification kinetics and bridge shape to the kinetics and shape of pure polymers. Their behavior can be rationalized in terms of simple linear combination of the behavior of pure polymer and excipient. Stress development in PVP-containing bridges, on the other hand, was significantly slower than stress development in both pure PVP and pure lactose bridges. It is important to note that it took about 5 days for the stress to develop and saturate in the PVP-containing bridge, while it saturated within only several hours in both bridges from pure components and HPC and HPMC. In addition, the shape of the PVP-containing bridge was different. All this indicates strong interaction between PVP and the non-polymeric excipient.

When comparing HPC- and HPMC-containing bridges, HPMC provided a slightly higher tensile strength both as pure binder and in a mixture with excipients. Stress development in HPMC was somewhat faster than in HPC. However, stresses that developed during solidification of HPMC-containing bridges exceeded periodically the strength of the material. This is evident from the sudden drop in exerted forces on the solidification curves. It was reported earlier that this decrease in force during solidification corresponds to partial bridge rupture (Tardos and Gupta, 1996). HPMC also seems to be more rigid than HPC. More important, however, is the fact that HPMC-containing materials appear to be much more brittle than those containing HPC, thus more prone to mechanical failure under stress. This explains our observations that some of the HPMC-containing bridges ruptured in a brittle fashion even under stresses developed during solidification. Thus, on a practical side, use of HPC appears to be advantageous as compared to HPMC.

While the above could be a somewhat simplified picture of the real phenomena, it provides enough insight into the process of binder-aided granulation and drying to enable at least a first approximation approach to obtain better and more resilient granules. HPC and lactose combinations are by far superior to any other mixture of ingredients tested in this study and unless there are specific reasons not to use them, they are preferred from both a micro-structural and strength point of view. Other excipients and polymers have all specific and somewhat different behavior that however can be used to advantage if the lactose–HPC system is unavailable.

Lastly, one important phenomenon that was not addressed in this study is the influence of shear forces during bridge formation. Shearing of the wet mass is clearly essential in an industrial granulation process. We expect that shear should provide better mixing of the granulating fluid and dry ingredients, assist in dissolution of soluble formulation components, and thus result in formation of liquid bridges that are nearly saturated with soluble dry components. In that regard, we would expect that composition of liquid bridges in granules of lactose–HPC based formulation obtained by high shear granulation would be closer to the 18% lactose–5% HPC samples in this study rather than to pure lactose or pure HPC bridges.

5. Conclusions

This study has clearly shown the crucial influence that relatively small amounts of polymeric binders such as HPC, HPMC and PVP have on the evolution, morphology and strength of drying and solidified bridges of pharmaceutical ingredients. It is evident from the information presented that interparticle bridges made of pure lactose or mannitol are weak even though these excipients are quite soluble in water and should, in principle, form extensive bridges as they dry and crystallize. In reality, while there is no shortage of bridge material, the crystallized bridge is polycrystalline, brittle and has low strength. Addition of small amounts of polymers modify drying behavior, shape and composition of the bridge and result in the formation of strong and tough bridges that impart great strength to the granule.

There is a significant difference between the way different binders interact with the excipients. Addition of lactose or mannitol to HPC and HPMC solutions does not affect either their drying behavior or kinetics, resulting in formation of a solid continuous phase that is strong and malleable and results in a strong interparticle bridge. PVP, in contrast, interacts more strongly

with the non-polymeric excipients, yielding a strong but more brittle bridge whose mechanical properties evolve much more slowly.

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