

# Formation of Hollow Granules from Hydrophobic Powders

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## ABSTRACT:

*Granulation of poorly wetting powders is a common problem in the pharmaceutical, minerals and fertilizer industries. It is usually assumed that good wetting is a prerequisite for good nucleation. Although this is generally true, robust granulations with poor wetting powders are possible. Recent investigation confirmed that nucleation can occur by spreading of hydrophobic sub-micron particles around the droplet, termed “solid spreading nucleation”. Moreover, nuclei formed consist of a consolidated powder shell and an empty core, and have extremely high porosity with adequate strength.*

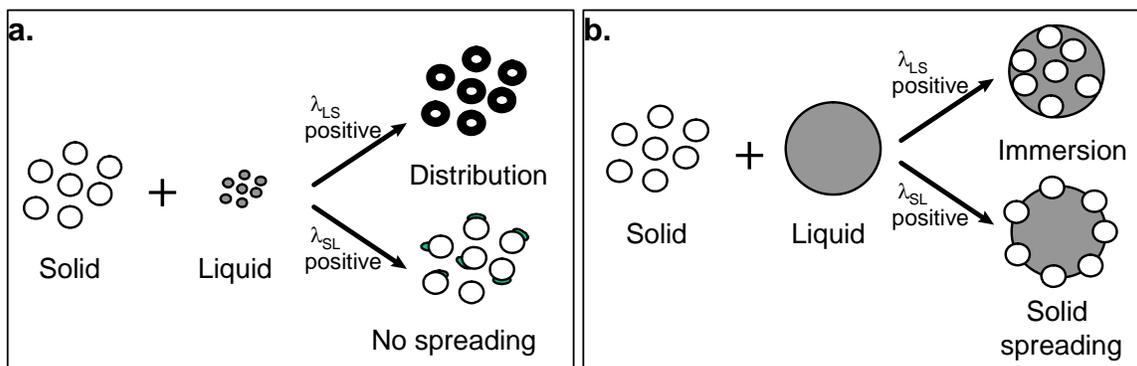
*In this study, single drop solid-spreading nucleation experiments were performed, where single drops of water and glycerin were produced using a microlitre syringe and placed onto loosely packed powder beds. Several powders including salicylic acid, 2-Ethoxybenzamide and three size grades of hydrophobic glass ballotini were used. Nucleus formation was observed via high speed video camera and a microscope. Preliminary experiments suggest that some bulk fluid motion is required for shell formation to occur, and that smaller particle size, lower fluid viscosity and higher kinetic energy during impact all favor the formation of a powder shell. Based on experimental results and observations, solid spreading nucleation mechanism and a model for surviving liquid marble was suggested.*

## 1. INTRODUCTION

Granulation of hydrophobic powders is a growing problem in the pharmaceutical industry. Conventional granulation theory assumes that the liquid spreads over the solid particles. However, it is known that hydrophobic powders may spread around the drop during agitation and/or rolling of fluid drops on a hydrophobic powder (Hapgood and Khanmohammadi 2007). It has been published recently that hydrophobic powder can be used in combination with water to produce stable and structurally strong spherical structures. (Aussillous and Quere 2006) describe “liquid marbles” formed from water droplets covered with hydrophobic lycopodium grains. Two groups (Farber *et al.* 2006; Forny *et al.* 2007) have independently applied the liquid marble approach to produce designer particle assemblies for industrial applications. These works showed how liquid marbles convert a normally problematic physiochemical property of hydrophobicity into a particle design advantage and show that liquid marbles can be produced using conventional granulation equipment.

The work by Farber *et al.* (2006) demonstrates that liquid marbles can be exploited as a precursor to hollow granules. Designing a hollow granule requires a sound understanding of controlling mechanisms of liquid marble formation via solid spreading nucleation (Farber *et al.* 2006). Spreading coefficients have been used by the pharmaceutical industry for many years to predict whether adequate wetting of the pharmaceutical powders will occur and have been suggested by Farber *et al.* as a potential driving force. The spreading coefficient  $\lambda$  is the difference between the work due to adhesion and cohesion (Rowe 1989) and indicates whether spreading (i.e. further replacement of the solid-vapor interface with a solid-liquid interface) is thermodynamically favorable. There are three possibilities in spreading between a solid and a liquid:

- a) The liquid may spread over the solid ( $\lambda_{LS}$ ) and create a surface film, representing the case of complete wetting;
- b) The solid spreads or adheres to the liquid ( $\lambda_{SL}$ ). The latter case will only occur if solid movement is physically possible, such as when the solid is in a powdered form. This is called *solid spreading nucleation* (Farber *et al.* 2006).
- c) Both the liquid and solid have high work of cohesion and no spreading occurs. This final case represents the case of complete non-wetting.



**Figure 1: Nucleation formation mechanisms as a function of spreading coefficients (Rowe 1989) when a) the liquid drops are smaller than the solid and b) when the solid particles are smaller than the liquid droplets (Farber *et al.* 2006)**

Studies of the effect of spreading coefficients on wet granulation (Zhang *et al.* 2002; Planinsek *et al.* 2000; Rowe 1989b; and Krycer and Pope 1983) represent only case (a) in Figure 1. Solid spreading nucleation where the powder is fine compared to the size of the liquid drops, i.e. case (b) in Figure 1, has been observed (Hapgood 2000; Simons and Fairbrother 2000), although the spreading coefficients were not measured to prove that the solid-over-liquid spreading coefficient  $\lambda_{SL}$  was the driving force. However, it is also possible that the observed motion of particles over the surface of the fluid drop is driven by a force unrelated to the spreading coefficient  $\lambda_{SL}$ . Alternative explanations for the observed particle motion include (see Figure 2).

1. Bulk motion within the drop caused by drop deformation and recoil motion after impact, which drives a corresponding surface flow around the drop entraining particles (Mahadevan and Pomeau 1999; Fujimoto *et al.* 2005).
2. Shear induced diffusion effects where the particle migrates towards the low shear zones at the top of the drop from the high shear region at the point of maximum drop deformation at impact (Leighton & Acrivos, 1987).
3. Lateral capillary forces or other colloidal interfacial effects known to physically stabilize emulsions.



**Figure 2: Alternate explanations for the movement of particles around the surface of the drop include surface flow as a result of shear flow at the impact point and/or bulk flow within the drop following impact and deformation.**

This paper presents the results of screening materials to find suitable systems that form liquid marbles and describes observations of the nucleation behavior of a single drop on a bed of hydrophobic powder.

## 2. EXPERIMENTAL

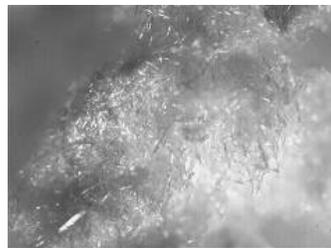
A loosely packed powder bed was formed by lightly sieving the powder through a sieve into a petri dish and subsequent leveling to produce a smooth powder surface. A loosely packed bed approximates the powder state in an agitated granulator (Hapgood *et al.* 2002). A 100 $\mu$ l Hamilton precision syringe with 22 gauge needle was positioned just above the bed surface. Drops were allowed to detach and gently fall 1-2mm before landing on the bed surface. A Stereo microscope (SMZ Series) with a 3MP camera operating at 30 frames per second was used to film a single drop of binder impinging on to the powder surface.

### 2.1 Materials

Glass ballotini spheres (Potters Industries Pty Ltd, Grade) in four size grades (AC, AE, AG, AH) were used. In order to make the glass beads hydrophobic, SIGMACOTE solution (chlorinated organopolysiloxane in heptane, Sigma Aldrich Pty Ltd.) was used. Glass beads are a good model material but other real model powders are also required. Two hydrophobic powders were used: Salicylic acid (99%ACS Reagent, Sigma Aldrich Pty Ltd) with a contact angle of 103° (Lerk *et al.* 1976) and 2-Ethoxybenzamide (97% Sigma Aldrich Pty Ltd) which has been used elsewhere as a model hydrophobic drug (Takano *et al.* 2003). The particle size distribution was analysed by dry laser diffraction using a Malvern Mastersizer 2000, although salicylic acid was measured by sieving. The true density of the particles was measured using Helium pycnometer (Micromeritics Accupyc 1330). Particle properties are summarised in Table 1 and Figure 3 shows optical microscope images of the needle-shaped salicylic acid and ethoxy-benzamide particles. We note that although the finest particle size specifications is for the AH ballotini grade, the particle size distributions was essentially identical to the AG grade.

**Table 1: Powder properties summary**

Powder Property	Salicylic acid	2-Ethoxy-Benzamide(EB)	Hydrophobic Glass Ballotini			
			AC	AE	AG	AH
d <sub>10</sub> ( $\mu$ m)	69	1.89	139	89	47	47
d <sub>50</sub> ( $\mu$ m)	132	4.67	191	121	66	65
d <sub>90</sub> ( $\mu$ m)	502	12.74	261	165	90	90
Surface mean d <sub>32</sub> ( $\mu$ m)	Not recorded	3.76	185	118	63	63
Volume mean d <sub>43</sub> ( $\mu$ m)	Not recorded	7.02	197	125	68	67
Malvern specific surface area(m <sup>2</sup> /kg)	Not recorded	1600	32	21	95	95
True Particle Density(g/cm <sup>3</sup> )	1.43	1.27	2.48	2.44	2.47	2.46
Molecular weight	138.12	165.19	60.1	60.1	60.1	60.1
Molecular Formula	2-(HO)C <sub>6</sub> H <sub>4</sub> CO <sub>2</sub> H	C <sub>2</sub> H <sub>5</sub> OC <sub>6</sub> H <sub>4</sub> CONH <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>	SiO <sub>2</sub>



**Figure 3: Optical microscope images of salicylic acid needles (left) and 2-ethoxybenzamide (right).**

Several different binder fluids were used: distilled water, four grades of poly-ethylene glycol (PEG200, PEG300, PEG400, and PEG600) and a 1% mass sodium dodecyl sulfate (SDS) solution. A summary of binder properties is given in Table 2.

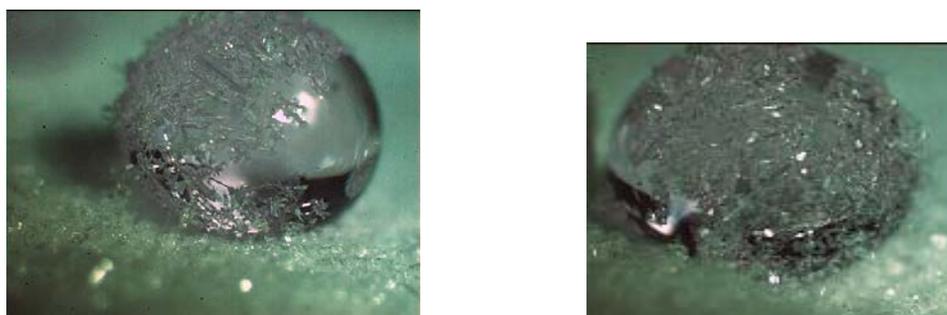
**Table 2: Granulating fluid properties at 20°C**

Granulating fluid	Density(g/mL)	Surface Tension(mN/m)	Viscosity (Pa.s)	Manufacturer
Distilled Water	1	72.0 <sup>a</sup>	1.0020	N/A
Glycerol	1.25 <sup>b</sup>	63.7 <sup>a</sup>	950 <sup>a</sup>	Fluka
PEG200	1.127 <sup>b</sup>	43.7 <sup>c</sup>	60 <sup>b</sup>	Sigma-Aldrich
PEG300	1.125 <sup>b</sup>	43.7 <sup>c</sup>	95 <sup>b</sup>	Fluka
PEG400	1.126 <sup>b</sup>	43.7 <sup>c</sup>	120 <sup>b</sup>	Sigma-Aldrich
PEG600	1.128 <sup>c</sup>	43.7 <sup>c</sup>	152.9 <sup>c</sup>	Fluka

a – Data from (a) Zajic and Buckton (1990) (b) Sigma-Aldrich. and (c) Hapgood, 2000.

### 3. RESULTS

Experiments initially focused on screening material combinations to find suitable systems for further study. Table 3 summarizes the experimental observations and some pictures of liquid marbles are shown in Figure 4. Water was able to form a liquid marble with all the powders tested, and glycerol was able to form liquid marbles with all powders except ethoxybenzamide. The addition of 1%SDS surfactant to the water eliminated liquid marble formation by reducing the contact angle below 90° allowing the drops to penetrate into the powder.



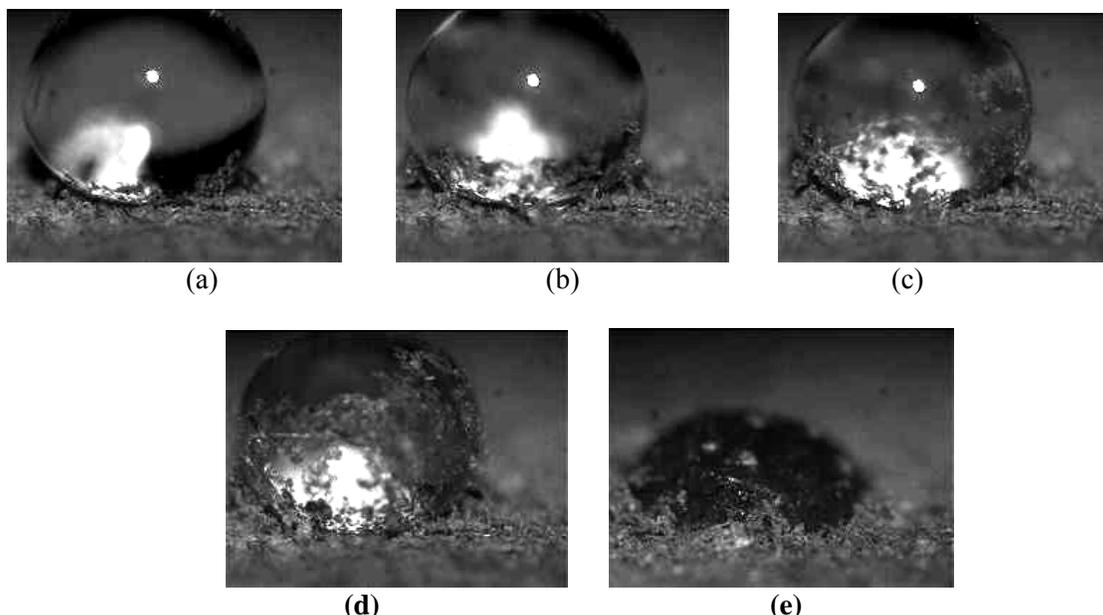
**Figure 4: Example of liquid marbles formed by solid spreading nucleation of salicylic acid powder over a water droplet.**

There are some interesting observations noted in Table 3. First, there appears to be a viscosity effect, where low viscosity PEG200 was able to form a liquid marble with AG and AH ballotini, but PEG300 and upwards were unsuccessful. However, the most viscous fluid tested so far, glycerol, was able to form liquid marbles which suggests that viscosity is a relatively minor effect compared to the surface chemistry of the powder – binder system. Second, there appears to be a particle size effect, where formation of liquid marbles using PEG200 was only successful on the two finest ballotini grades – AG and AH – which had identical particle size distributions as noted earlier. This implies either that the driving force (currently not known) is not strong enough to carry the largest ballotini particles around the drop surface, or that there is a drop to particle size ratio criterion for liquid marble formation.

During the experiments, it appears to be possible to temporarily form liquid marbles from systems with contact angles less than 90° that initially form a powder layer on the drop exterior but then penetrate completely into the powder bed. This is shown in Figure 5 for water on food-grade cinnamon powder. Further investigation, including contact angle measurements, is underway.

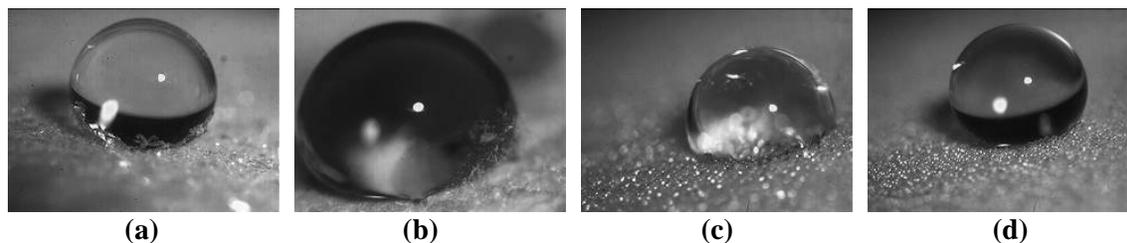
**Table 3: Summary of liquid marble formation experiments**

<b>Binder</b> <b>Powder</b>	<b>PEG200</b>	<b>PEG300</b>	<b>PEG400</b>	<b>PEG600</b>	<b>Distilled Water</b>	<b>Glycerol</b>	<b>Water+ 1% SDS</b>
Salicylic acid	No	No	No	No	✓	✓	No
2-Ethoxy-benzamide	No	No	No	No	✓	No	No
Glass Ballotini(AC)	No	No	No	No	✓	✓	No
Glass Ballotini (AE)	No	No	No	No	✓	✓	No
Glass Ballotini (AG)	✓	No	No	No	✓	✓	No
Glass Ballotini (AH)	✓	No	No	No	✓	✓	No

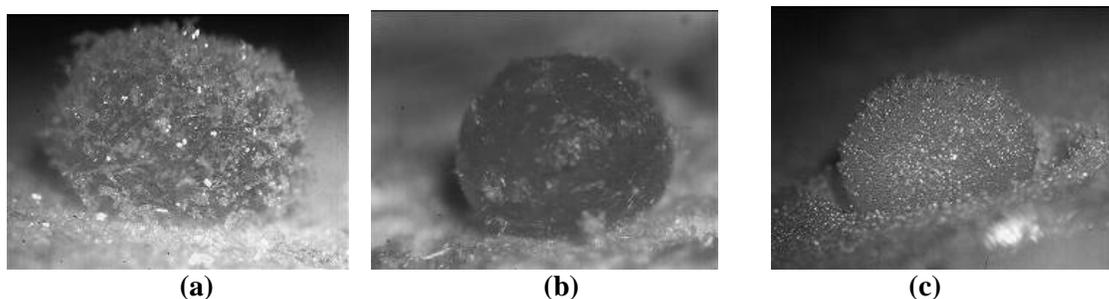


**Figure 5: Water on cinnamon powder showing initial stages of liquid marble formation, after (a) impact; (b) 3 Sec. ; (c) 6 Sec. ; (d) 10 Sec. followed by penetration into the powder bed; (e) after 3 Min.**

The experiments in Table 3 were performed by allowing the drop to fall a short distance of approximately 1-2mm. An increased tendency to form a liquid marble was observed when the drop rolled or deformed during impact. A second series of experiments was performed where the drops of water and glycerol were placed extremely gently onto the powder bed to avoid bulk motion within the drop interior due to impact or rolling. Figure 6 shows that there is no surface coverage when a water droplet is carefully placed on several particles, presumably because no bulk motion is created within the droplet which entrains the particles in the surface flow. The same behavior was also observed for careful placement of glycerol droplets.



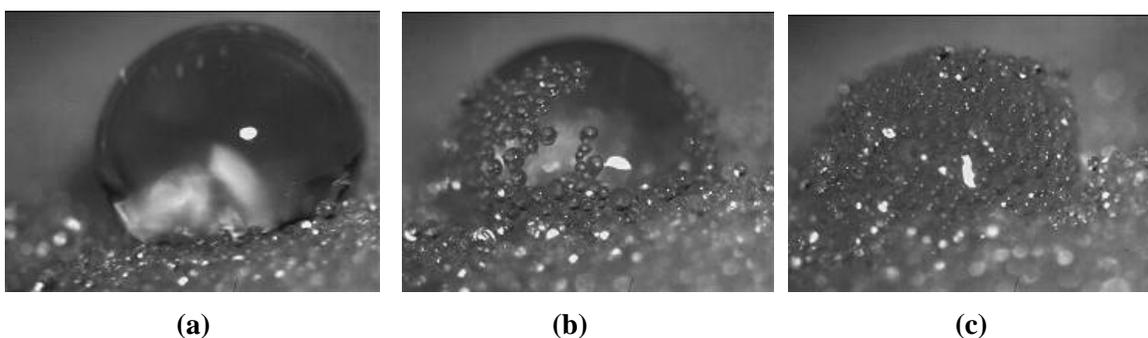
**Figure 6: Careful placement of a water droplet on (a) salicylic acid (b) 2-Ethoxy Benzamide (c) AE glass ballotini (d) AG glass ballotini shows no liquid marble formation.**



**Figure 7: Effect of rolling or shaking on surface coverage. (a) water on salicylic acid after shaking (b) water on 2-Ethoxy Benzamide after rolling and (c) glycerol after shaking on AH ballotini.**

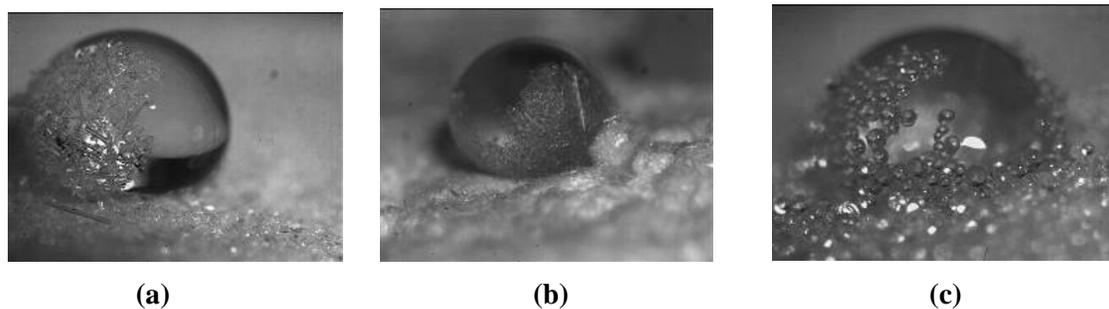
Alternatively, the particles can be spread over the uncovered droplet by shaking the petri dish. Figure 7 shows a much higher level of surface coverage compared to the careful placement experiment shown in Figure 6. Moreover, if the droplet is allowed to roll on the surface, the droplet will become covered with particles, as described by Aussillous and Quere (2006) and shown in Figure 7 (b).

To test whether bulk motion is responsible for the formation of the powder shell, the drop release height was increased to 15cm and 30cm. Figure 8 shows the gradual increase in surface coverage for a water-AC ballotini system as the drop height is increased. Since the physiochemical properties of these experiments are constant, the kinetic energy of the drop appears to determine the extent of shell formation. In practical granulation situations, we presume that the drop surface is instantly covered with powder due to the highly agitated powder motion in the fluidized bed or mixer granulator.



**Figure 8: Liquid marble formation using water and hydrophobic AC ballotini powder from (a) 0cm height (b) 15cm height and (c) higher than 30cm level**

When the drop is only partially covered with powder, the powder is not evenly distributed over the powder surface, but instead accumulates to form a powder sheet (refer to Figure 9). Individual particles move across the drop surface until they aggregate into a film. This phenomenon is caused by attractive lateral capillary immersion forces and was also described by Forny *et al.* (2007).

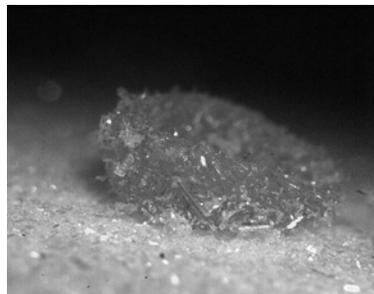


**Figure 9: Partly formed powder sheets due to lateral capillary forces. Water droplet on (a) Salicylic acid, (b) 2-Ethoxy Benzamide (c) hydrophobic AC ballotini**

#### 4. DISCUSSION

The solid-over-liquid spreading coefficient  $\lambda_{LS}$  (Rowe 1989) as shown in Figure 1 may provide a quantitative method to predict whether a given formulation will form liquid marbles. However, our results suggest that bulk motion of the drop, due either to rolling or impact, is required for solid spreading nucleation to occur. It is also possible that solid spreading motion is driven entirely by a physical flow mechanism (Figure 2), where the degree of surface coverage is proportional to the size of the bulk flow generated within the drop, and that the spreading coefficients are not applicable to liquid marble formation. Surface energy measurements by inverse gas chromatography are underway to determine whether  $\lambda_{LS}$  can be used as a predictive tool.

All of the hollow granules formed in these studies eventually collapsed into hemispheres (see Figure 10). Only multi-component formulations can produce inter-particulate bonds to stabilize hollow granules once the template drop has been removed during drying. To date, only one investigation (Farber *et al.* 2006) into liquid marbles and solid spreading nucleation has used a multi-component formulation of powders. All other studies have used a single fluid on a neat hydrophobic powder (Aussillous and Quere 2006; Forny *et al.* 2007). This is also an area requiring significant further investigation.



**Figure 10: Water-salicylic acid granule collapse into hemisphere during air drying.**

In order for a stable, spherical, liquid marble to form from a single drop via solid spreading nucleation, we outline a series of steps that must occur:

1. A single drop must be formed that is much larger than the size of the powder particles (i.e.  $d_d \gg d_p$ ) (Schæfer and Mathiesen 1996; Tardos *et al.* 1997) and to allow for critical packing fraction to be reached within a high shear region localised along some portion of the drop interface, but small enough to form a spherical drop rather than a distorted pool or puddle i.e. Bond number  $Bo < 1$  (Aussillous and Quere 2006).
2. The drop must land on the powder and survive the impact without breaking or shattering into smaller droplets i.e. Weber number  $We < 1000$  (Agland and Iveson 1999) and Ohnesorge number  $Oh > 0.05$  (Bartolo *et al.* 2005).
3. The fluid must have a contact angle  $\theta$  greater than  $90^\circ$  with the powder to prevent penetration of the drop into the powder bed (Myers 1991; Hapgood *et al.* 2000).
4. The powder must spread around the air-liquid interface of the drop to form a shell – driven either through impact induced surface flows (Mahadevan and Pomeau 1999; Fujimoto *et al.* 2005), or shear induced migration, as discussed earlier.
5. The powder must be able to self-assemble into a sufficiently dense layer to prevent contact of the drop interior with a supporting surface. (Forny *et al.* 2007).

If any of these conditions are not fulfilled, a liquid marble will not be formed. In addition, in order to maintain small individual drop templates, the dimensionless spray flux must be low (Litster *et al.* 2001). Under low spray flux conditions the granule size would be controlled by the atomized drop size i.e. the drop controlled nucleation regime (Hapgood *et al.* 2003).

For a stable, spherical hollow granule to form from a single drop, additional steps must occur:

6. In an agitated powder mass, the liquid marble must be sufficiently strong to withstand the stresses experienced within in the agitated bed and subsequent standard powder handling operations.
7. The concentration and distribution of hydrophilic excipients must not negatively affect hollow granule formation, strength or stability.
8. The multi-component powder shell must be sufficiently strong to be self-supporting after the template drop has been removed in order to avoid collapse during drying and subsequent standard powder handling operations.

The controlling groups for these final three steps to form hollow granules are currently unknown but are expected to be complex functions of powder and liquid physiochemical properties and packing arrangements of multi-component particles. This area is the subject of further research by the authors.

## 5. CONCLUSION

We report here the first stage of ongoing work studying the granulation of hydrophobic powders by the solid spreading nucleation mechanism. Several combinations of hydrophobic powders and binder fluids have been shown to exhibit solid spreading nucleation and to form “liquid marbles” (Aussillous and Quere 2006). The liquid marble structure seems superficially consistent with the long established spreading coefficients (Rowe 1989), although we also propose an alternate mechanism where bulk motion within the drop creates a corresponding surface flow which entrains particles, creating a shell.

Preliminary experiments suggest that some bulk fluid motion is required for shell formation to occur, and that smaller particle size, lower fluid viscosity and higher kinetic energy during impact all favor the formation of a powder shell. Some unexpected behaviour was reported, where a powder shell initially began to form but was not stable and the drop then penetrated into the powder bed. Finally, we proposed a framework for liquid marble formation by outlining the sequential steps and where possible the controlling groups for each step. However, the ultimate aim of this ongoing research project is to follow the lead of Farber *et al.* (2006) and dry the liquid marbles to produce hollow granules suitable for pharmaceutical applications.

## 6. ACKNOWLEDGEMENTS

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