Supplementary information for

Confinement in printed droplets: effect on crystallisation of d-mannitol polymorphs

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Content:

Experimental:

Imaging

Light microscopy Images of crystals were taken by either Leica Galen III microscope (Leica Microsystems, Wetzlar GmbH) connected to the camera of an iPhone 5s (Apple Inc, USA) using HookUpz Universal adaptor (Carson Optical, USA), or Nikon microphot-FXA light microscope (LM) was used with an Infinity 2 digital camera and capture application software (version 3.7.5). Videos of drying microliter droplets were undertaken using a LeicaADM 2700M microscope connected to a FP82HT Mettler Toledo Instruments heating stage unit and a FP90 Mettler Toledo Instruments central processor unit. Images of 0.2 µL drop of mannitol solution (0.5 M) on glass slide were recorded while drying at room temperature The Studio86 Design Capture software (version 4.0.1) was used to record and capture thermal events in real time.

Scanning electron microscopy images were collected on printed samples with a scanning electron microscope (SEM, Quanta 200 FEG, FEI, Netherlands). Samples were prepared by sputter-coating with gold for 3 min (Quorum model Q150).

Evaporation rate determination

Data were recorded with a Sorption Analyser (Q5000 SA, TA Instruments, Waters, USA) with nitrogen as a carrier gas (200mL/min for the humidity chamber and 10mL/min for the balance). The test solution (2, 5 or 10 µL) was placed in a metalised quartz pan using a 20 µL Gilson pipette and was kept isothermally at 25 °C and a humidity of 0 or 50% RH until constant mass (< 0.01% weight change). The change of mass with time was recorded with a microbalance (≤ ± 0.1% accuracy and 0.01 µg resolution) while two precise mass flow controllers controlled the relative humidity by mixing saturated and dry carrier gas. The overall evaporation rate was calculated in µg/s and is reported as mean ± standard deviation (SD of three measurements.

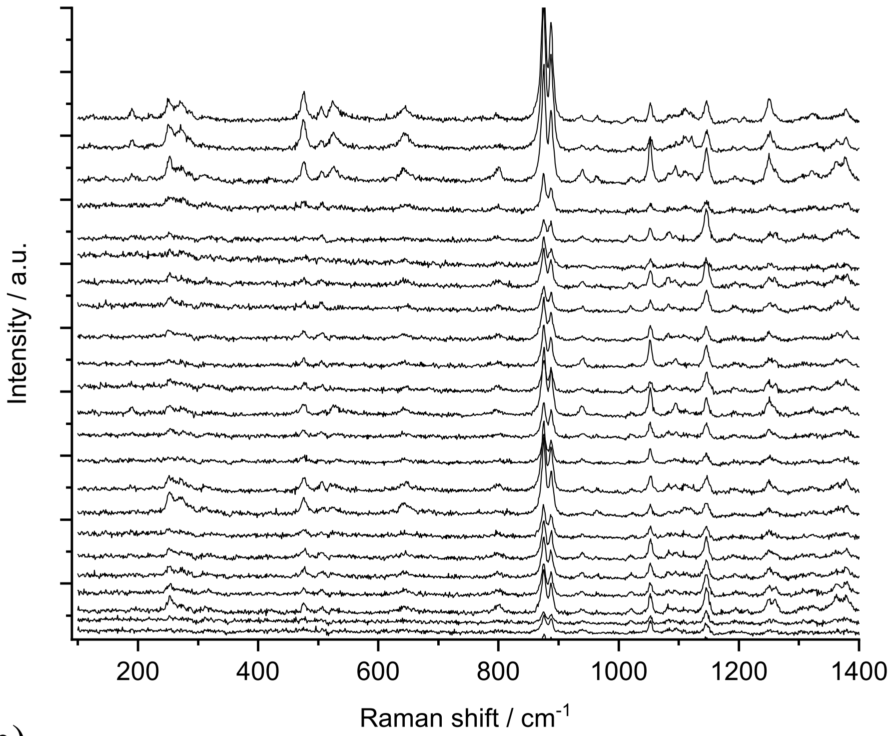
Contact angle measurement

Constant contact angle was measured by the sessile drop method using an FTA1000 Analyzer System (First Ten Angstrom, Inc., USA). A droplet (10 µL) was placed onto the substrate and the contact angle was calculated with the dedicated software (Fta32 Video, 2.1, First Ten Angstrom, Inc., USA). Measurements were performed in triplicate and values are reported as mean ± SD.

Table S1 Crystallographic Data of D-mannitol polymorphs

	Alpha form	**Beta form**	**Delta form**
CSD Refcode	DMANTL08	DMANTL09	DMANTL10
Crystal System	Orthorhombic	Orthorhombic	Monoclinic
Space Group (Å)	$P\ 2_1\ 2_1\ 2_1$	$P\ 2_1\ 2_1\ 2_1$	$P\ 2_1$
a	4.8653(10)	5.5381(10)	4.899(2)
b	8.873(2)	8.580(2)	18.268(6)
c	18.739(3)	16.795(5)	5.043(2)
α	90	90	90
β	90	90	118.39
γ	90	90	90
Cell Volume ($Å^3$)	808.959	798.046	397.034
Z	4	4	2
ρ_{calc} (g/cm^3)	1.496	1.516	1.524
Polymorphic relation	Monotropic		
		Enantiotropic	

(a)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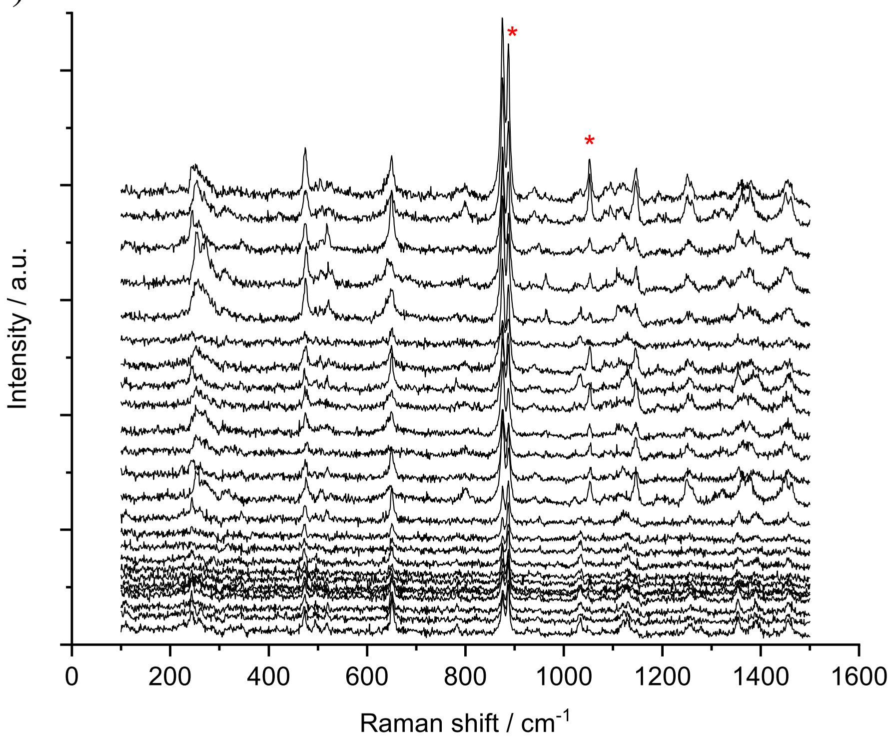
600
800
1000
1200
1400
Raman shift / cm-1

(b)


*
*
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1600
Raman shift / cm-1

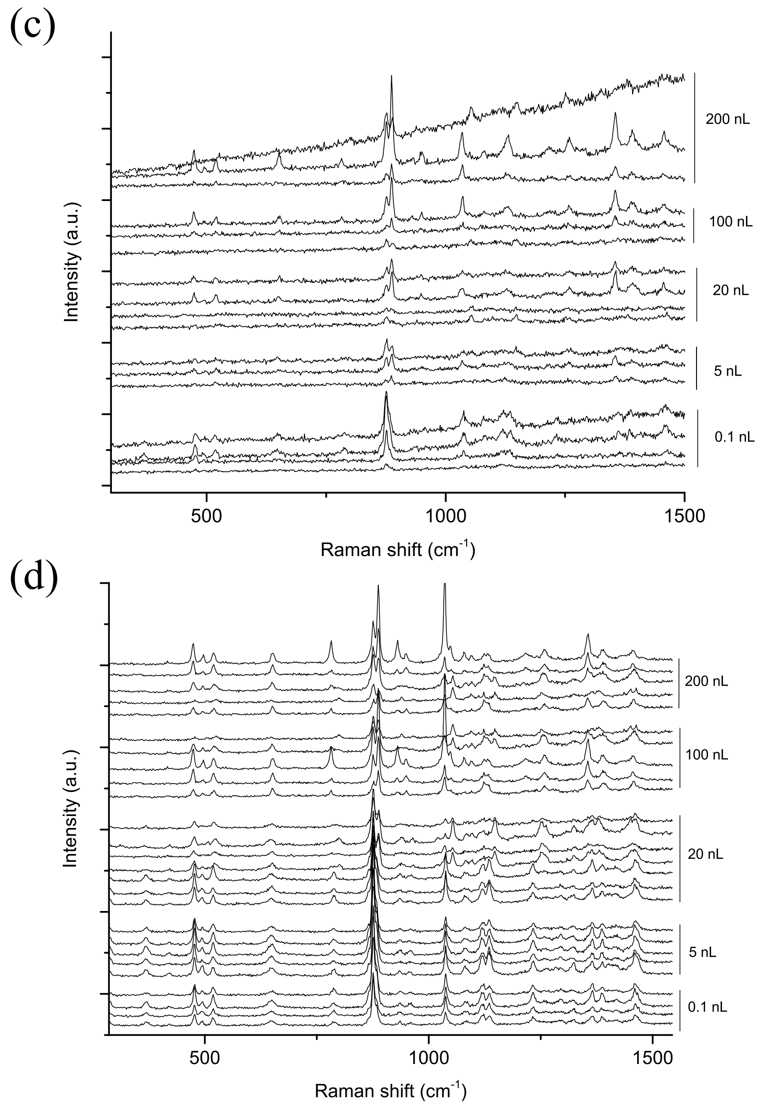


Fig. S1. Raman spectra from crystals formed in printed drops of 100 nL (a and b) and up to 200 nL (0.2 µL) (c and d) on glass (a and c) and (b and d) aluminium foil.

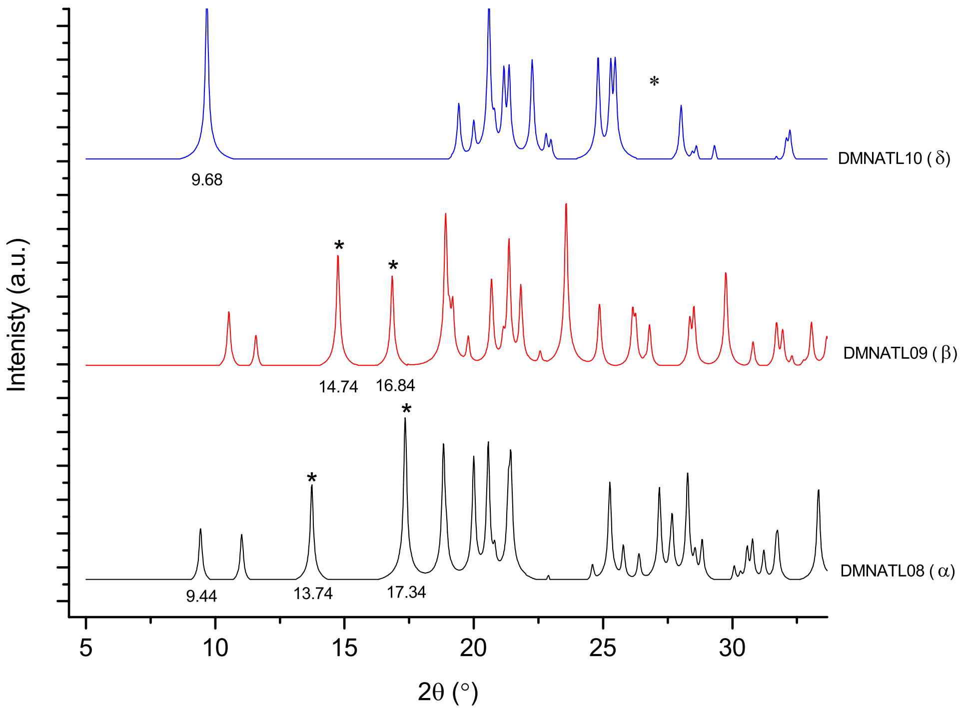


Fig. S2 Calculated PXRD patterns for d-mannitol forms α, β and δ with the characteristic peaks indicated with (*).

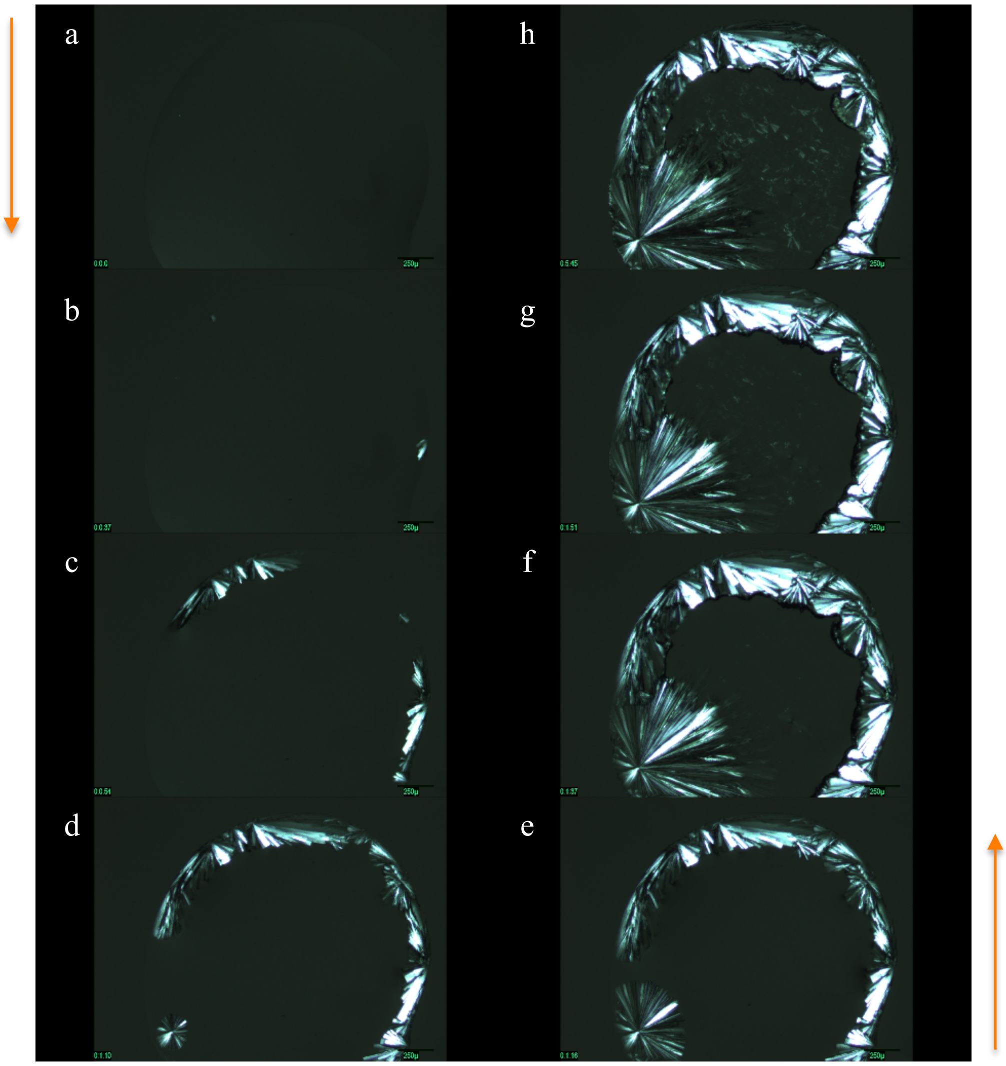


Fig. S3. PLM images of crystals formed in 0.2 µL drop on glass showing crystallisation starting from the edge of the drop resulting in the formation of coffee-ring phenomenon.

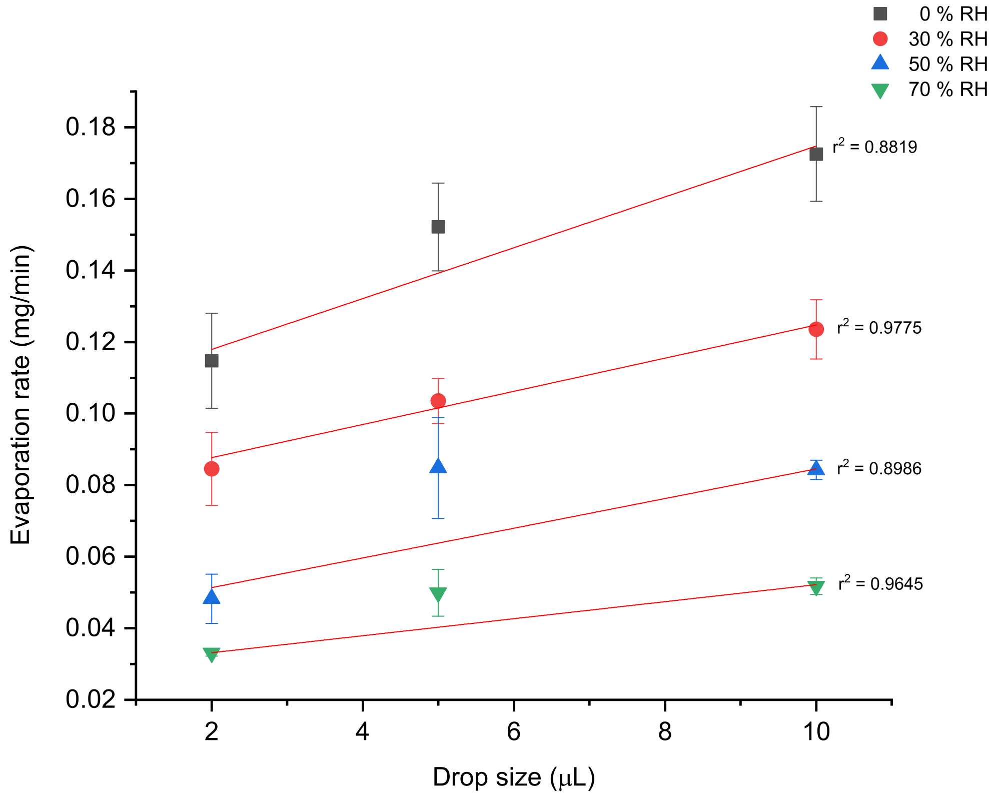


Fig. S4. Evaporation rate of mannitol droplets at different relative humidity values measured with dynamic vapour sorption.

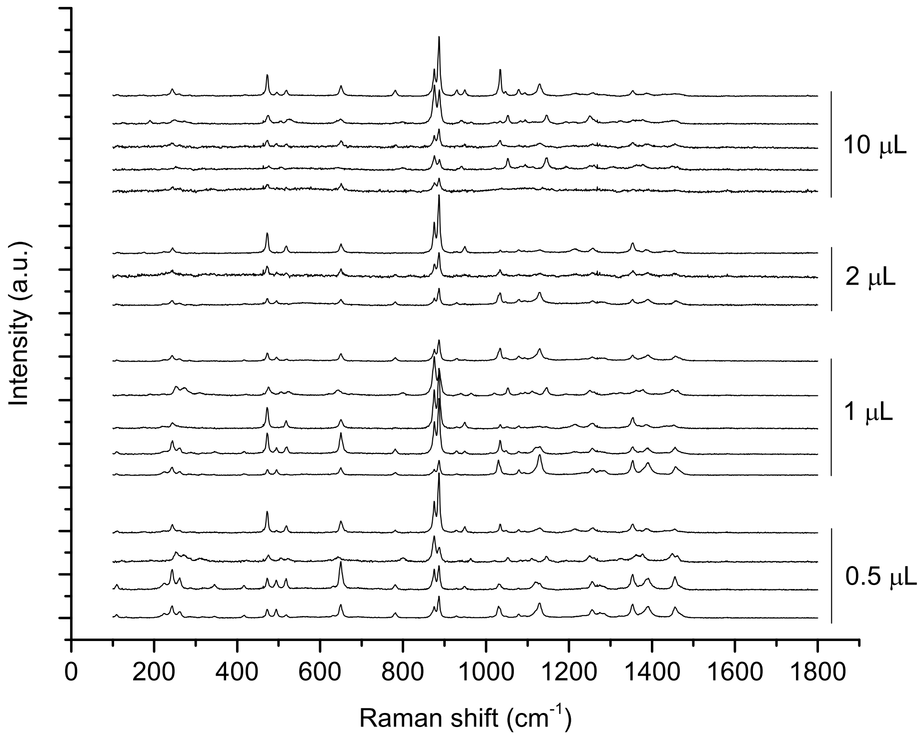
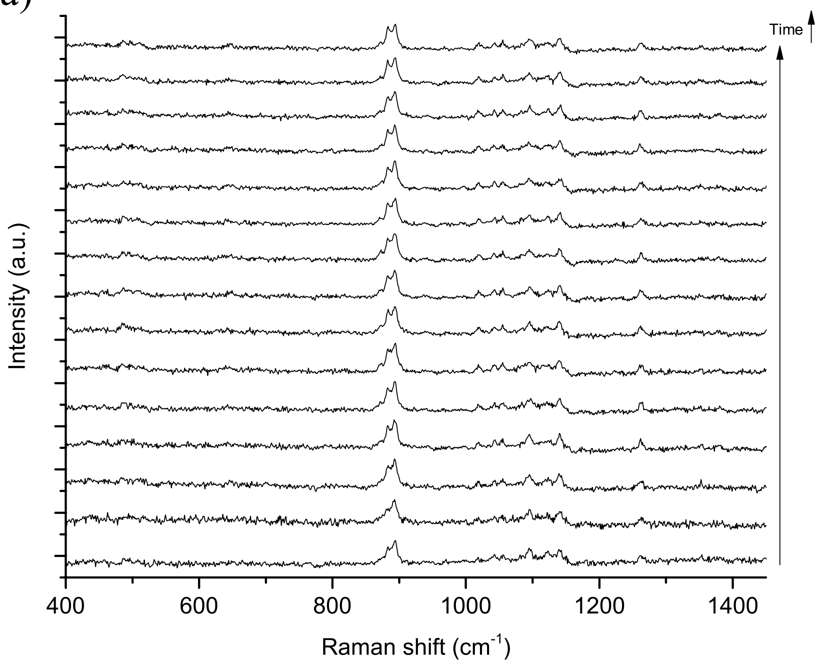


Fig. S5. Raman spectra from crystals formed in 0.5 to 10 μL drops on glass slide showing a mixture of α and δ forms.

(a)



(b)

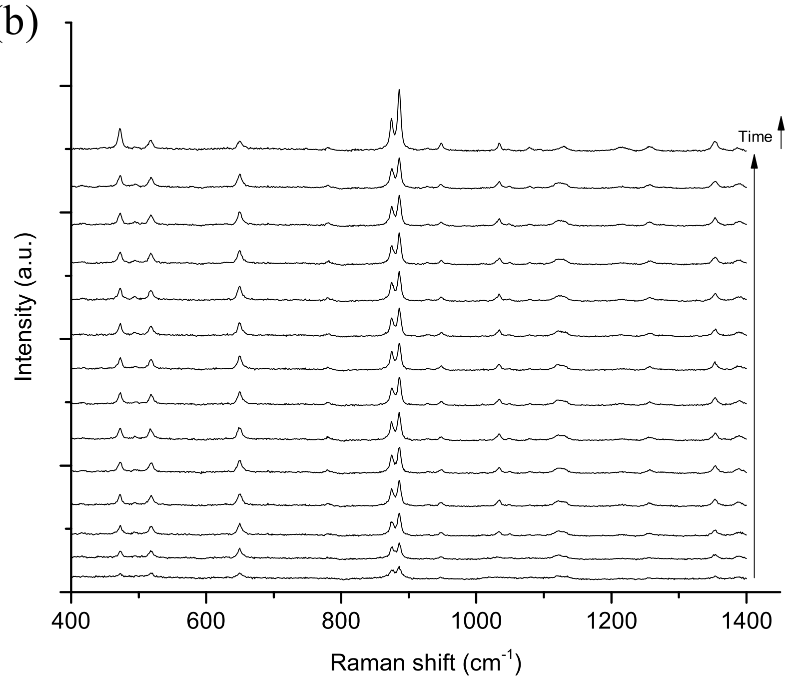
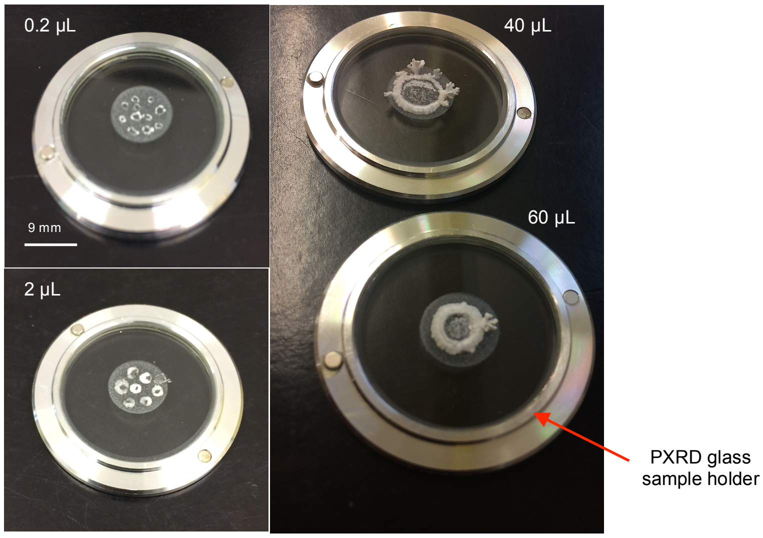


Fig. S6 Raman spectra during drying of 0.2 uL drop on (a) glass and (b) aluminium, showing characteristic peaks for alpha form.

(a)



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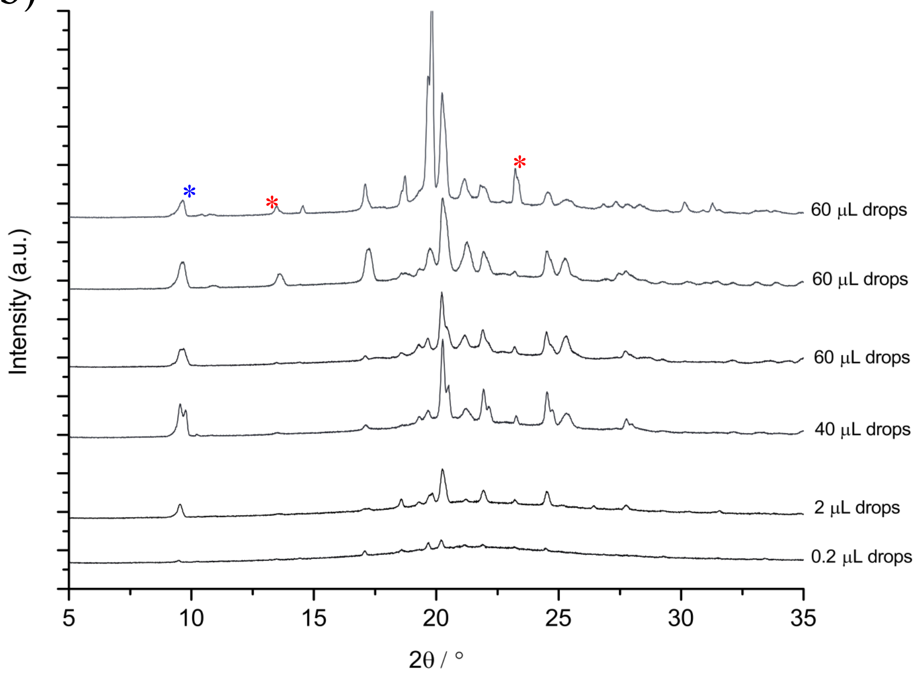


Fig. S7. (a) Images of microlitre drops on glass holder and (b) PXRD patterns from crystalline material formed upon drying showing characteristic peaks for delta (blue starlet) and beta (red starlet).

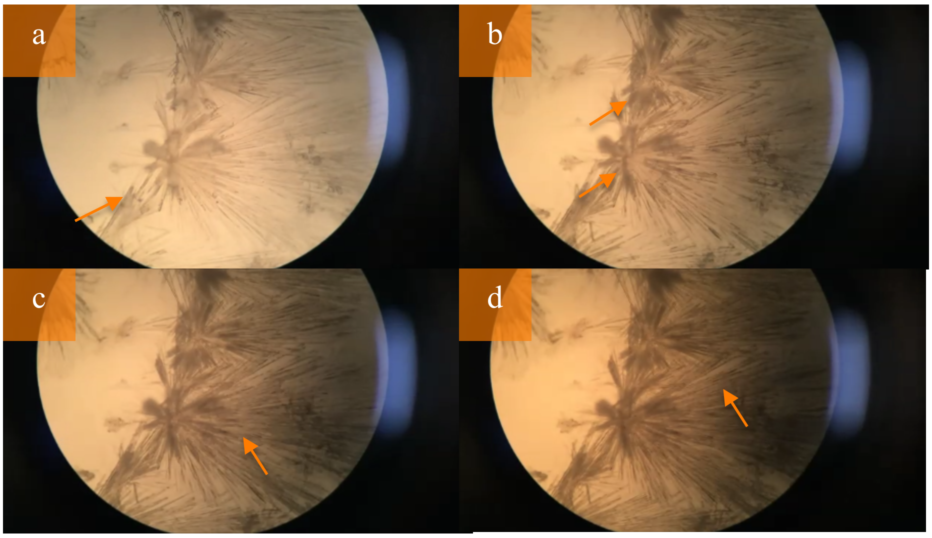
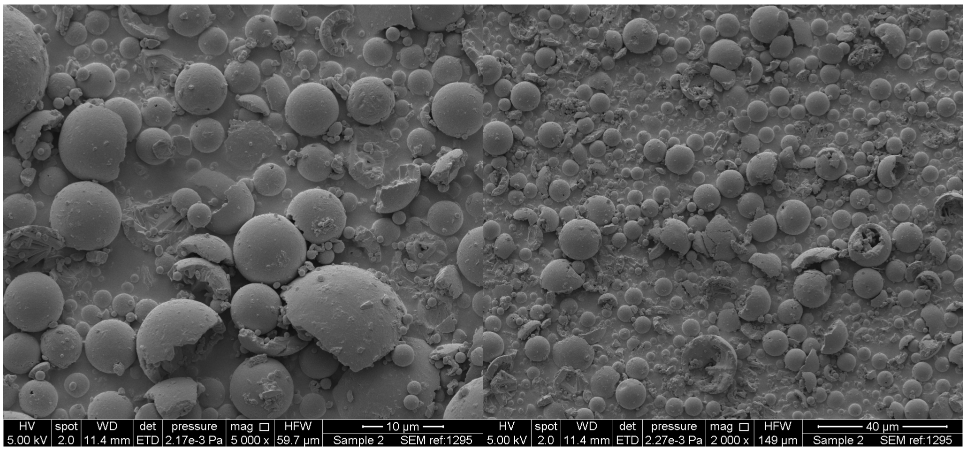


Fig. S8. Light microscopy images of conversion of mannitol crystals formed in a 10 µL drop drying on glass slide (arrows indicate areas with noticeable change).

(a)



(b)

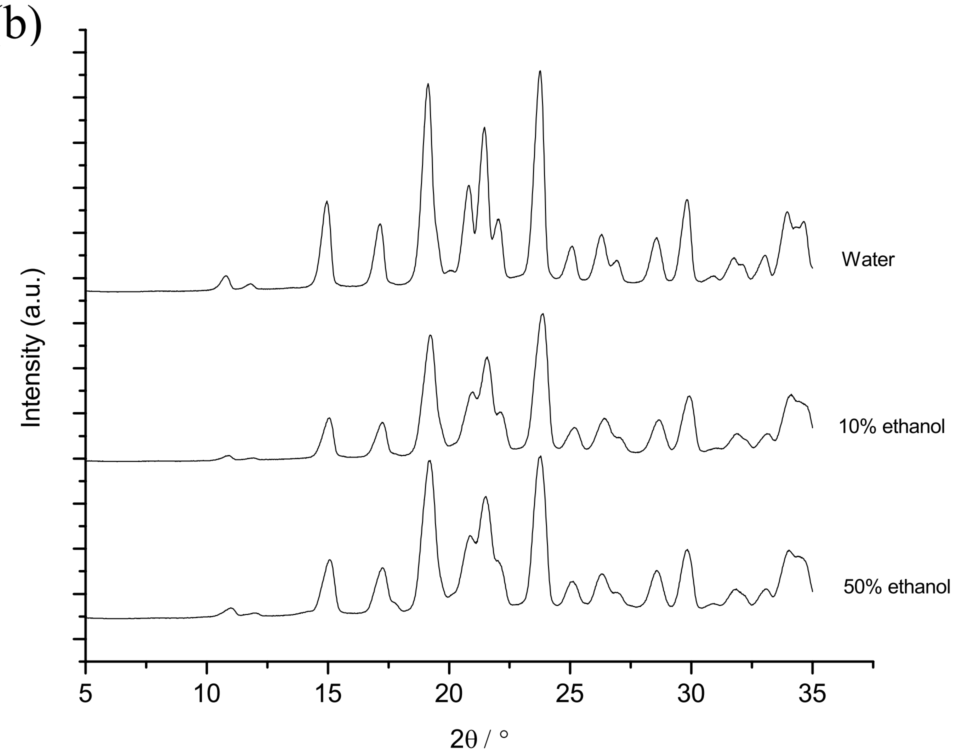


Fig. S9. a) SEM images and b) PXRD patterns of spray dried mannitol samples from either water or ethanol and water mixture.

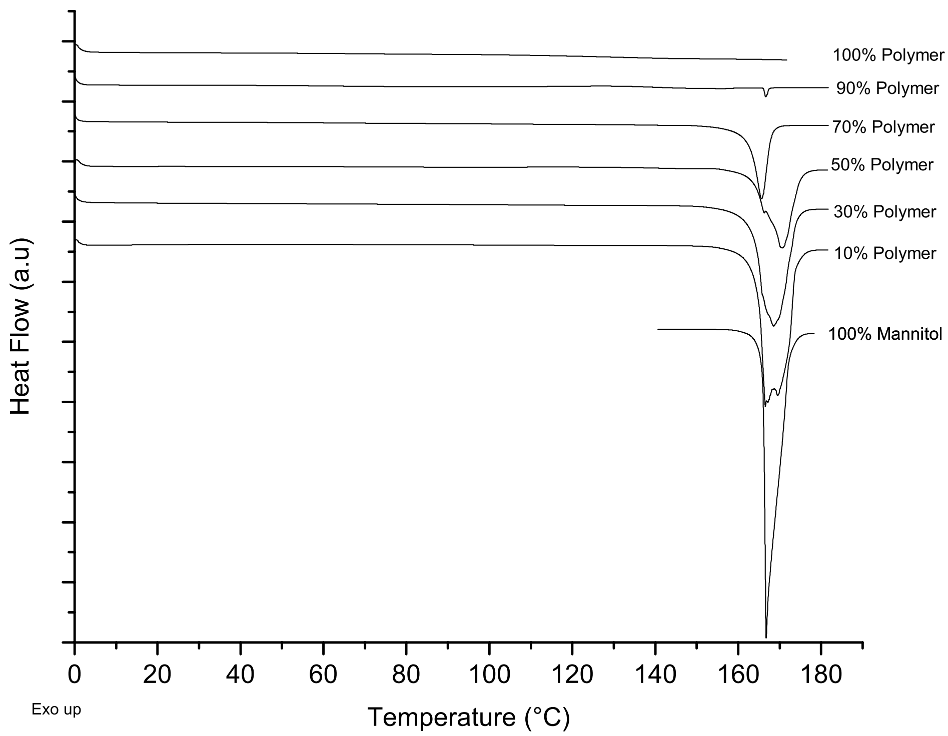


Fig. S10. DSC thermograms of spray dried mannitol with Eudragit polymer (10 to 90% w/w)