Porosimetry as a Predictor of Dissolution Rate for Capsule Formulations Prepared by Dry, and Wet Granulation Techniques

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Purpose

Some techniques for making solid oral dosage forms are wet granulation, dry granulation and direct blending (no granulation) (1,2). These compounding techniques all yield different particle characteristics. Some granulation characteristics that can vary include particle size, flow, density and porosity. These physical characteristics impact downstream processability.

Variations in process techniques also have a significant impact on finished dosage form quality attributes. One important product quality attribute that can vary is dissolution rate. The goal of the study was to establish whether a correlation existed between the porosity of the resulting granulations and dissolution rate.

	Formulation	A	B	C	D
	Granulation	Dry Roller Compacted	HS Wet	HS Wet	HS Wet
Granulating Fluid (H_2O)	(w/w)	NA	12%	12%	10%
Wet Massing Time	(min)	NA	8.25	2.0	2.0
Total Intrusion Volume	(mL/g)	0.4884	0.563	0.5849	1.0776
Total Pore Area	(m^2/g)	18.793	12.227	10.859	20.149
AVG Pore Diameter (4V/A)	(µm)	0.1040	0.1842	0.2154	0.2139
Bulk Density at 0.52 psia	(g/mL)	0.8916	0.8239	0.8156	0.5904

Table 1. Porosimetry analysis results

	50mg Capsule							
Batch	A (Dry Roller Compacted)		B (HS Wet)		C (Milled)		D (Milled)	
Time (min)	%Release	RSD%	%Release	RSD%	%Release	RSD%	%Release	RSD%
5	11.4	25.1	11.1	33.9	4.1	34.5	7.0	29.0
10	22.5	20.2	31.3	32.6	12.1	22.2	18.3	23.6
15	34.8	18.7	44.9	27.7	19.7	16.1	28.5	19.1
30	69.9	16.7	74.0	8.1	44.2	13.0	61.9	25.4
45	82.8	10.1	84.2	3.7	64.8	13.1	82.0	12.2
60	86.9	2.5	88.3	4.1	83.2	12.4	90.6	2.1
90	88.9	2.5	90.8	1.2	94.0	5.7	93.6	3.0
120	89.9	2.4	91.5	1.2	98.6	3.8	92.8	3.6

Table 2a. 50mg dissolution performance data.

	100mg Capsule							
Batch	A (Dry Roller Compacted)		B (HS Wet)		C (Milled)		D (Milled)	
Time (min)	%Release	RSD%	%Release	RSD%	%Release	RSD%	%Release	RSD%
5	1.6	15.4	3.0	34.5	3.0	22.7	5.5	32.5
10	12.2	7.6	9.0	27.3	9.2	12.8	23.0	37.2
15	12.3	7.6	15.8	23.6	16.6	13.1	39.5	25.0
30	30.7	10.1	47.0	22.5	51.6	14.3	66.3	14.7
45	50.5	5.7	74.2	12.2	84.6	5.2	77.7	9.2
60	75.8	12.3	85.7	5.7	93.9	2.2	83.0	6.8
90	93.1	7.5	89.2	4.5	96.1	2.2	87.7	4.6
120	98.9	5.3	89.6	4.3	95.6	2.3	90.0	3.1

Table 2b. 100mg dissolution performance data.

Methods

Formulations: A common formulation was used to prepare four prototype batches which differed in their granulation process parameters. Capsule granulations for an immediate release dose were prepared by high shear (HS) wet and dry granulation techniques. Granulations were filled into capsule shells by hand (Profill, Torpac) and tested for dissolution rate.

Dry Granulation: Batch A prepared utilizing a TF Mini Roller Compactor (Vector Corporation) with a compaction force of 1500psi.

HS Wet Granulation: Batches B, C, and D prepared in a lab-scale GMX.01 High-Shear Granulator (Vector Corporation).

HS wet granulations differed in the amount of granulating fluid (water) and wet-massing times as follows: Batch B utilized a quantity of granulating fluid equivalent to 12% (w/w) of the granulator charge and a wet-massing time of 8.25 minutes; Batch C incorporated the same 12% (w/w) granulating fluid quantity, but used a wet-massing time of 2 minutes; Batch D used a quantity of granulating fluid equivalent to 10% (w/w) of the granulator charge and a 2 minute wet-massing time.

The High-shear wet granulations were dried in a MFL.01 Micro-Flo Coater Fluid Bed (Vector Corporation) to an LOD that was ±1% of the initial LOD of the granulator charge prior to the addition of granulating fluid.

Milling: Granulations (A-D) were then milled using a Model 197 CoMil (Quadro) and milled granulations blended with extragranular excipients (glidant and lubricant) in a V-shell blender (Patterson Kelly). Final blends were manually encapsulated (ProFill, Torpac) as 50mg and 100mg strength capsules in size 4 and size 2 gelatin capsule shells respectively.

Mercury intrusion porosimetry: This testing involves placing the sample in a special sample cup (penetrometer), then surrounding the sample with mercury. Mercury is a non-wetting liquid to most materials and resists entering voids, doing so only when pressure is applied. The pressure at which mercury enters a pore is inversely proportional to the size of the opening to the void. As mercury is forced to enter pores within the sample material, it is depleted from a capillary stem reservoir connected to the sample cup. The incremental volume depleted after each pressure change is determined by measuring the change in capacitance of the stem. This intrusion volume is recorded with the corresponding pressure or pore size.

Dissolution analysis of capsules was performed with USP Apparatus II. Quantitation of drug release was performed by HPLC.

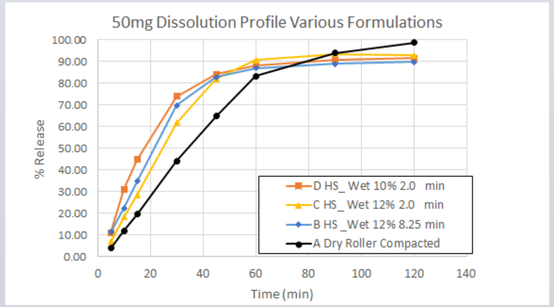

Figure 1a. 50mg dissolution profiles various formulations.

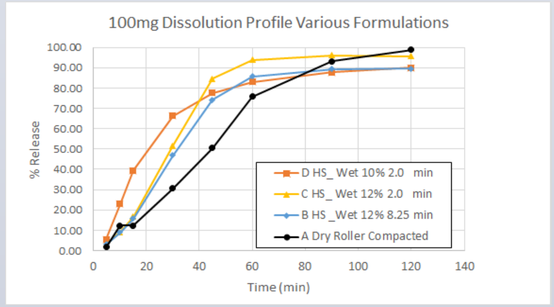

Figure 1b. 100mg dissolution profiles various formulations.

Results

Porosimetry analysis results are provided in Table 1. Granulations produced by different techniques resulted in capsules exhibiting different dissolution profiles, Figures 1a & b. Dissolution performance data is shown in Tables 2 a & b. From the porosimetry results, average pore diameter was found to correlate well with the dissolution profiles (Figure 2a & b) at multiple time points on the dissolution curve.

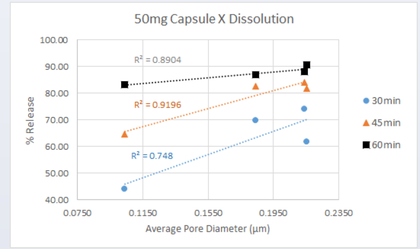

Figure 2a. 50mg correlating release (%) to average pore diameter (µm).

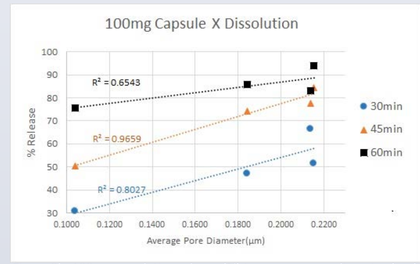

Figure 2b. 100mg correlating release (%) to average pore diameter (µm).

Conclusions

Porosimetry is a useful tool for evaluation of granulations manufactured by different methods and may be helpful in determination of the most suitable process for a given target product profile. In addition, given current QBD (2,3) requirements for establishing the design space for manufacturing unit operations, demonstration of control of particle porosity may provide additional (along with dissolution rate) supporting evidence that the process is under control within the defined design space.

References

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