Development of a novel continuous filtration unit for pharmaceutical process development and manufacturing: modelling and experimental approach to estimate cake properties

EPSRC Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallisation

CMAC

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PARAMETERS INTERACTING DURING FILTRATION:

System considered	Properties
Crystal/cake	• Particle size distribution (PSD) • Particle shape (AR) • Porosity (ε) • Permeability (k)
Suspension	• Wettability (Θ)
Fluid/thermo dynamic	• Viscosity (μ) • Pressure (ΔP)

Important cake properties (Tien,2002; Tien and Bai, 2003):

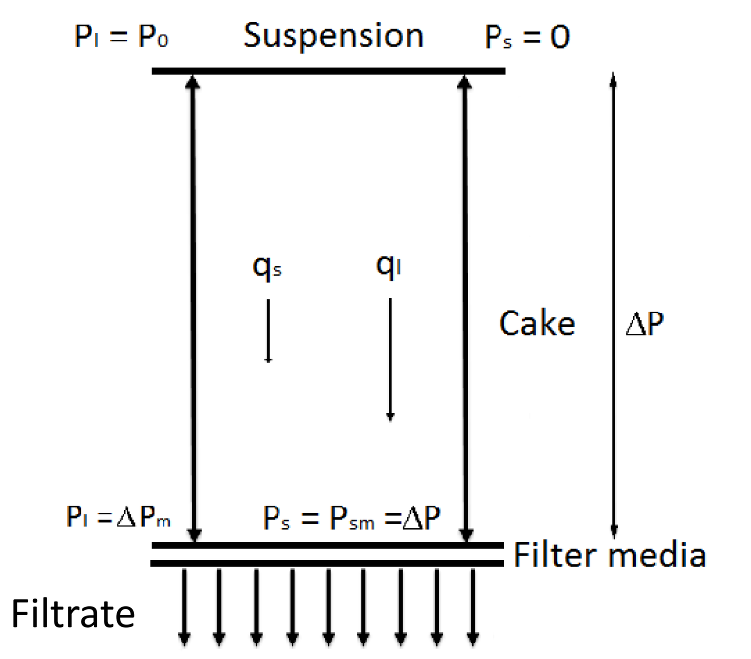
$\varepsilon = \varepsilon(P_s)$

$k = k(\varepsilon)$

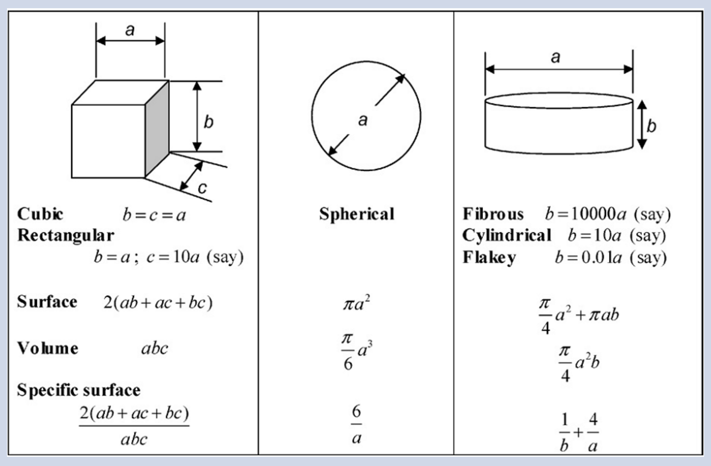
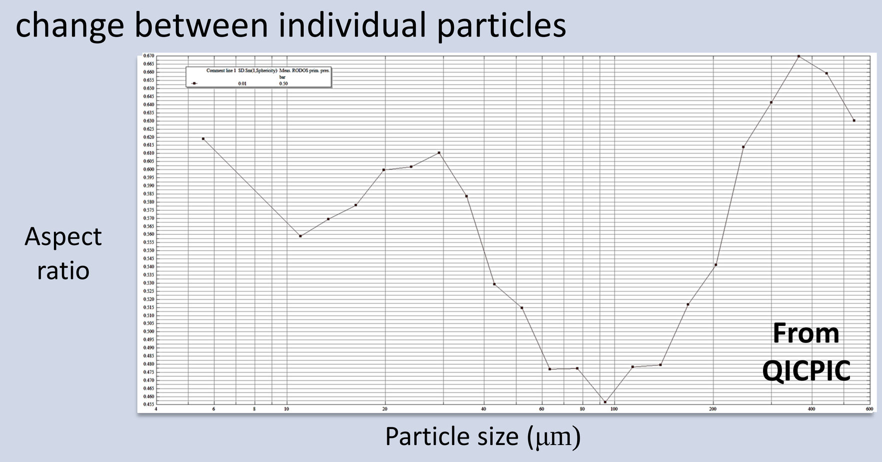
where $P_s = P_s(P_l)$

From conventional filtration theory (Darcy's equation):

$$\frac{q_l}{1-\varepsilon} - \frac{q_s}{\varepsilon} = \frac{1}{1-\varepsilon}\frac{k}{\mu}\frac{dP}{dx}$$



- Which modelling approach can be used to describe cake properties?
- Which cake properties can be evaluated by experimental approach?

Model	Benefit	Lack
Wakeman, 2007: $\alpha_{average} = \frac{1}{\rho_s(1-\varepsilon)k} \propto \frac{1}{x_{sv}^2}$ where $S_0 = \frac{6}{x_{sv}}$ $for\ spherical\ particles$ Where xsv is the surface-volume mean diameter and S_0 is the volume specific surface from Carman-Kozeny equation	• Easy approach • S_0 and xsv calculated experimentally • S_0 is related to shape of particles (Wakeman, 2007) 	• Particles shape and surface are more irregular and shape can change between individual particles  • Solvents-particle interactions are not considered
Murugesan, 2012: $\alpha = \alpha_0\left(\frac{\Delta P}{\Delta P_{ref}}\right)^n$	• α_0 and n are empirical constants • n represents the compressibility index of the cake when it is pressurized: 1. n > 1 highly compressible cake (Darcy's equation is no longer valid) 2. 0 < n < 1 moderately compressible cake (Darcy's equation remains valid) 3. n = 0 incompressible cake (Darcy's equation valid) • P_{ref} is an arbitrary differential pressure under which α = α_0	• Particle shape is not considered • Solvents-particle interactions are not considered
Constitutive relationships of filter cake properties (Tien and Bai, 2003): $\varepsilon = \varepsilon^0\left(1+\frac{P_s}{P_a}\right)^{\beta}$ $k = k^0\left(1+\frac{P_s}{P_a}\right)^{-\delta}$ $\alpha = \frac{1}{\varepsilon\rho_s k} = \alpha^0\left(1+\frac{P_s}{P_a}\right)^n$	• n = δ-β, ε^0, k^0, α^0 , β, δ and Pa are empirical constant	• Particle shape is not considered • Solvents-particle interactions are not considered
Carman-Kozeny approach (Wakeman, 2007): $\alpha_{average} = \frac{180}{\rho_s x_{sv}^2}\left(\frac{1-\varepsilon}{\varepsilon^3}\right)$ **Yelshin, 2002 approach:** $\alpha_{average} = \frac{36\,k\,(1-\varepsilon)}{\rho_s x_{sv}^2 \varepsilon^3} = \frac{36\,k_0\,T^2\,(1-\varepsilon)}{\rho_s x_{sv}^2 \varepsilon^3}$	• xsv calculated experimentally • Carman-Kozeny, k is defined as constant, where T is the tortuosity of the cake and k₀ is the shape coefficient depending to the cross section of capillary pore	• Particles shape and surface are more irregular and shape can change from particles • Solvents-particle interactions are not considered
Digipac™ software/Fractal approach (Jin, 2015): to model structure and predict the properties of particle systems (eg packing density, particle orientation, contact statistics, distribution of individual components, etc.)	Allows evaluation of real particle shapes to describe system porosity	• For Digipac™: requires X-Ray Tomography or desktop laser scanning to scan particle shape which is then converted in CAD files • High computational time requirement

EXPERIMENTAL DATA FROM BIOTAGE AND AWL CFD20 UNIT:

Equations used:

Darcy's first derivative from constant pressure filtration (Beckmann, 2013):

$$\frac{t}{V} = \frac{\mu\alpha}{A\,\Delta P}V + \frac{\mu\,Rm}{A\,\Delta P}$$

Where cake resistance (α) and media resistance (Rm) are extrapolated.

Cake void fraction:

$$Void\ fraction = 1 - \frac{\rho_{cake}}{\rho_{bulk\ (from\ helium\ picnometer)}}$$

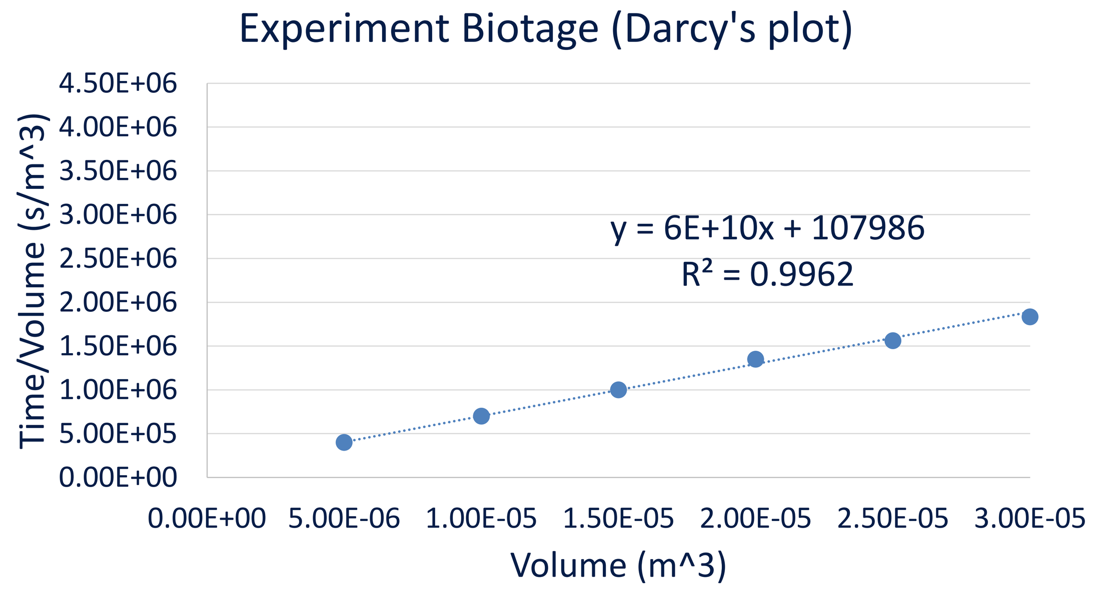
Experiment setup and slurry properties:

PARACEAMOL GRADE	D10 (μm)	D50 (μm)	D90 (μm)
Micronised	4.3	26.7	66.8

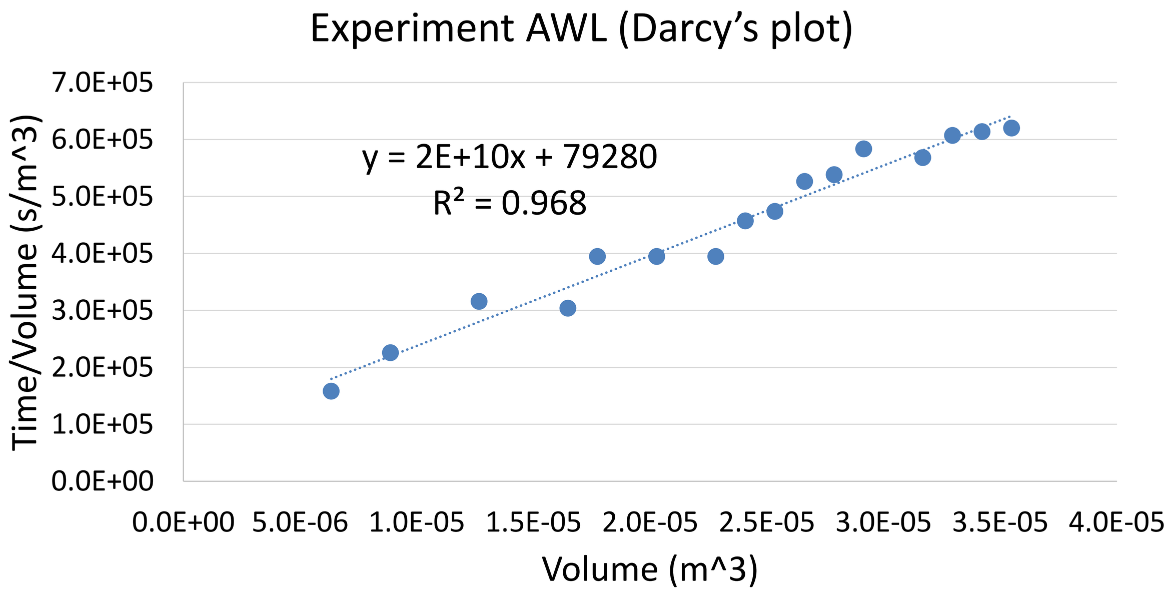
MATERIAL	VISCOSITY (Pa s)	DENSITY (g/cm³)
Ethanol	0.0012	0.789
Saturated ethanol solution	0.0147	0.84

EXPERIMENT Biotage and AWL	MATERIAL
Grade	Micronised (M)
Dose	50ml
Stirrer velocity	300rpm
Vacuum applied during filtration	800mbar
Vacuum applied during wash 1	800mbar
Vacuum applied during wash 2	800mbar
Hold time before washing	60s
Dry time	5min
Deliquor mode	Dryland
Wash mode	Dryland

Experiment Biotage (Darcy's plot)

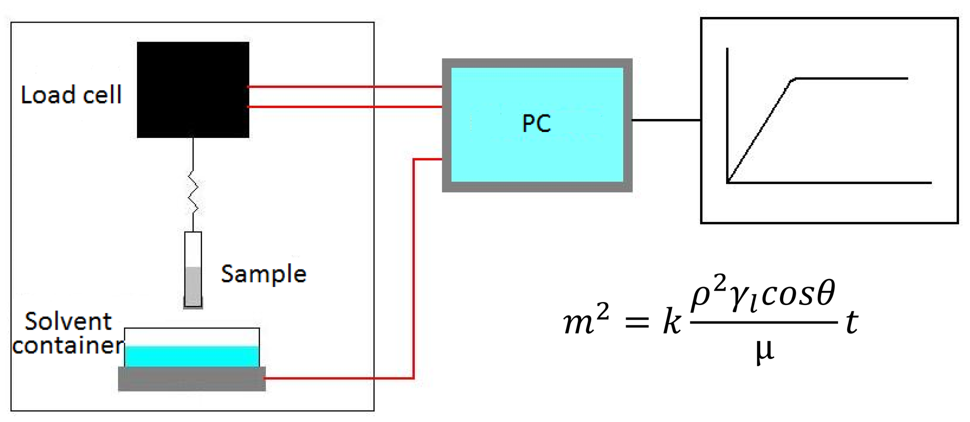


Experiment AWL (Darcy's plot)



	Exp Biotage	Exp AWL
α (m/kg)	2.05E+08	3.35E+08
Rm (1/m)	1.87E+09	2.54E+07
ε	0.44	-
Volume pore (ml)	5.5	-
Xsv (from QICPIC analysis)	41.78	57.07
S0 (Wakeman, 2007)	0.14	0.10
k	7.31E-12 (Wakeman, 2007) 4.88 E-09 (Ripperger, 2012)	- 2.98E-09 (Ripperger, 2012)
n (compressibility index)	0.2327	0.2327

WASHBURN METHOD TO STUDY SOLUTE-SOLVENT INTERACTIONS:



$$m^2 = k\frac{\rho^2\gamma_l\cos\theta}{\mu}t$$

Symbol	Definition
m	Increasing weight of the powder
ε	Packed powder porosity
ρ	Liquid density
R	Inner radius of the tube
γl	Surface energy of the liquid
t	Time of capillary rise
k	Geometric coefficient
ϴ	Contact angle
R	Inner radius of the tube

Washburn method (Siebold, 1997): the liquid is drawn up through the powder bed by capillary rise forces (Poiseuille flow); The mass increment during time can be used to calculate contact angle that is occurring in powder capillaries during the liquid rise.

	Mass (Kg)	Time (s)	K	ϴ (°)
Heptane	7.78E-4	50	5.39E-16	73.94
Anisole	1.25E-3	29	1.95E-15	REF
Acetonitrile	6.08E-4	30	2.34E-16	83.11
Acetone	7.38E-4	38	3.6E-16	79.37
Iso-propyl acetate	1.06E-3	40	1.14E-15	54.32
TBME	8.66E-4	26	2.56E-16	82.46

CONCLUSIONS:

- Models evaluated are listed in order of accuracy of data generation and parameter accessibility. Digipac™ and fractal approach are the only ones able to describe real particle shape and so real porosity system, but they do not consider solute-solvent interactions.
- Darcy output are different from the two units, mainly due to difficulties to control vacuum with AWL unit (communal lab vacuum used for initial AWL experiments was prone to fluctuations).
- Cake porosity could not be calculated for the first prototype AWL unit due to early stage vision system. New vision system allows both volume of cake and filtrate to be determined online.
- Washburn method can be use to establish correlation solute-solvent by considering the wettability of system.
- Future investigation using gPROMS will allow investigation to establish which model best fits the experimental data.