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Process modelling and simulation for continuous pharmaceutical manufacturing of ibuprofen

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ABSTRACT

Pharmaceutical corporations face rapidly rising process research and development (R&D) as well as production costs due to globalised competition. Batch production processes are dominant in the pharmaceutical industry and have multiple advantages, including equipment flexibility, high-fidelity quality control and the ability to recall specific batches; they however suffer disadvantages such as limited heat transfer and mixing scalability and low operational asset efficiency. Continuous Pharmaceutical Manufacturing (CPM) has a documented potential to reduce cost, as continuous production techniques can be easier to scale up and can be designed to be more efficient in terms of both solvent and energy use: therefore, it is both timely and important to explore the expanding feasibility limits of this emerging technology. The literature has been extensively surveyed in order to identify a series of candidate Active Pharmaceutical Ingredients (API) for flowsheet synthesis, process modelling and mass balance simulation toward rapid assessment of CPM potential. Ibuprofen [2-(4-isobutylphenyl)propanoic acid], the widely used non-steroidal anti-inflammatory drug (NSAID), has emerged as an ideal CPM candidate because it is in high global demand and can generate significant profit margins. The flowsheet is based on a published organic synthesis pathway and produces 50 kg of ibuprofen annually using three plug flow reactors (PFRs) in series, followed by a final separation for purification. Kinetic and thermodynamic parameter estimation modelling has been employed in order to compute essential data for design, and all PFR reactors have been designed based on reported conversions of feed and intermediate organic molecules in the respective organic synthesis reactions. Theoretically computed reactor designs are in good agreement with experimental prototypes constructed for the same organic synthesis, as well as in with previously reported CPM systems. The developed continuous final separation performs very well in accordance with green chemistry principles, with relatively low environmental impact (E-factor = 25.4).

1. Introduction

Batch manufacturing processes feature advantages including equipment usage versatility, flexible production planning and scheduling, and a wide range of attainable products, and have dominated the pharmaceutical industry for a number of decades; they still are considerably more preferable due to regulatory and licensing considerations and the option to quickly recall specific batches of products (Plumb, 2005). Nevertheless, they have several disadvantages: new processes are often difficult to scale up to production level due to poor heat transfer and mixing (potentially resulting in unacceptable product

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Nomenclature

Latin letters

A	Shomate equation parameter
a_i	heat capacity group contribution estimation parameter for functional group i
a^s	pure solid component activity
B	Shomate equation parameter
b_i	heat capacity group contribution estimation parameter for functional group i
C	Shomate equation parameter
C_A	concentration of molecule A, mol L^{-1}
$C_{A,0}$	initial concentration of molecule A, mol L^{-1}
C_i	group coefficient for functional group i in the total phase change entropy group additivity estimation method
C_P	specific heat capacity at constant pressure, J mol^{-1} K^{-1}
c_i	heat capacity group contribution estimation parameter for functional group i
D	Shomate equation parameter
d_i	heat capacity group contribution estimation parameter for functional group i
E	Shomate equation parameter
G_i	contribution from one functional group i to the total phase change entropy in the group additivity estimation method, J mol^{-1} K^{-1}
h_{f0}	constant used in estimating the standard enthalpy of formation $\Delta^\circ H_f$
h_{1i}	standard enthalpy of formation group contribution of a single first-order group i
h_{2j}	standard enthalpy of formation group contribution of a single second-order group j
ID	internal diameter, mm
k'	pseudo-first-order reaction rate constant, h^{-1}
k_i	rate constant of reaction i, L mol^{-1} h^{-1}
L_i	UNIFAC compound parameter of r, q and z
M_j	number of j second-order functional groups
m_{API}	mass of recovered API
m_{bpd}	mass of byproducts
m_{ur}	mass of unreacted reagents
m_{us}	mass of unrecovered solvent
m_{uAPI}	mass of unrecovered API
MW	molecular weight, g mol^{-1}
m_{waste}	mass of waste
N_i	number of i first-order functional groups
n_{CH_2}	number of consecutive CH_2 groups
n_i	number of i functional groups
Q_k	UNIFAC surface area parameter for functional group k
q_i	UNIFAC parameter for molecule i, a measure of van der Waals molecular surface area
R	Universal gas constant, 8.3144 J mol^{-1} K^{-1}
R^2	coefficient of determination
R_k	UNIFAC volume parameter for functional group k
r_A	rate of reaction of molecule A, mol l^{-1} h^{-1}
r_i	UNIFAC parameter for molecule i, a measure of van der Waals volume
T	temperature, K
T°	standard ambient temperature, 298.15 K
T_{feed}	feed temperature, °C
T_{PFR}	reactor temperature, °C
T_{fus}	melting (fusion) point temperature, K
t	time, h
U_{mn}	UNIFAC energy interaction between groups m and n
X_A	conversion of molecule A at time t
$X_{A,f}$	final conversion of molecule A
x_i	mole fraction of molecule i
x_m	UNIFAC mole fraction of group m
x_i^{sat}	mole fraction at saturation (solubility)
z	UNIFAC system coordination number (default value: 10)

Greek letters

Γ_k	UNIFAC residual group activity coefficient for group k
$\Gamma_k^{(i)}$	UNIFAC residual group activity coefficient in a reference solution of 100% i molecules
γ_i	activity coefficient of component i
γ_i^c	UNIFAC combinatorial component of γ_i
γ_i^r	UNIFAC residual component of γ_i
γ_i^{sat}	activity coefficient of component i at saturation
$\Delta^\circ H_f$	standard enthalpy of formation, J mol^{-1}
ΔH_{fus}	enthalpy of fusion, J mol^{-1}
$\Delta^\circ H_{rxn}$	standard reaction enthalpy, J mol^{-1}
ΔH_{rxn}	reaction enthalpy, J mol^{-1}
$\Delta_m^{T_{fus}} H_{tpce}$	total phase change enthalpy, J mol^{-1}
ΔS_{fus}	entropy of fusion, J mol^{-1} K^{-1}
$\Delta_0^{T_{fus}} S_{tpce}$	total phase change entropy, J mol^{-1} K^{-1}
θ_i	UNIFAC molar-weighted area fractional component for molecule i
θ_m	UNIFAC summation of area fraction of group m over all different groups
$\upsilon_k^{(i)}$	UNIFAC number of occurrences of functional group k in molecule i
τ_i	residence time in reactor i, h
ϕ_i	UNIFAC molar-weighted segment fractional component molecule i
Ψ_{mn}	UNIFAC group energy interaction parameter

quality) and efficiency can be very low with high volumes of unrecovered solvent (Anderson, 2012; Gernaey et al., 2012). Batch production plants also require significant intermediate storage capacity between process stages, resulting in large inventories of feedstock organic chemicals and sensitive intermediates.

In recent years, pharmaceutical firms have faced mounting pressure to reduce ever-increasing R&D as well as production costs (Fig. 1). The commercialisation of new drugs can require up to $1.8 billion in total per product, a high cost which has been steadily increasing (Fig. 2). Competition from generic drug manufacturers also increases the pressure on pharmaceutical firms (Behr et al., 2004). Taking into account clinical approval and patent duration, by the time the product reaches the market half of its patent life may have expired; once this occurs, the original developer may lose up to 90% of market share to generic manufacturers (Plumb, 2005).

Continuous Pharmaceutical Manufacturing (CPM) offers many advantages: lower costs, reduced waste, decreased time-to-market for new drugs, continuous flow reactors can deliver significantly higher yields, and solvent and energy waste