Chemical Engineering Science 129 (2015) 25–33

Contents lists available at ScienceDirect

Chemical Engineering Science

journal homepage: www.elsevier.com/locate/ces

# Evaluation of a structural mechanics model to predict the effect of inserts in the bed support of chromatographic columns

Spyridon Gerontas [a], Tian Lan [b], Martina Micheletti [b], Nigel J. Titchener-Hooker [a,b,*]

[a] EPSRC Centre for Innovative Manufacturing in Emergent Macromolecular Therapies, Bernard Katz Building, Gordon Street, London WC1H 0AH, UK
[b] The Advanced Centre for Biochemical Engineering, Department of Biochemical Engineering, University College London, Bernard Katz Building, Gordon Street, London WC1H 0AH, UK

## HIGHLIGHTS

- Inserts are placed within chromatography columns to enhance wall support.
- The impact of column inserts is captured by structural mechanics models.
- Simulations are shown to be in good agreement with experimental data.
- The model helps selecting dimensions of inserts to increase column linear velocity.

## ARTICLE INFO

*Article history:*
Received 27 May 2014
Received in revised form
26 January 2015
Accepted 8 February 2015
Available online 16 February 2015

*Keywords:*
Biot's theory
Chromatography
Column insert
Compression
Critical velocity
Wall support

## ABSTRACT

Cell culture titres are expected to increase still further over the forthcoming years. This imposes challenges for downstream processing including the potential need to use larger volumes of chromatography resins. Such a move could create throughput bottlenecks because of the compressible nature of many commercially available resins, which makes the operation of columns with diameters beyond 2 m infeasible due to resin collapse. The use of cylindrical inserts of negligible thickness has been proposed in the literature as a way to enhance the level of wall support, allowing higher superficial flow velocities to be applied and hence larger diameter columns to be used. In this study, a structural mechanics model has been developed to evaluate the effect of inserts on the column pressure drop and flow characteristics. Simulations were shown to be in good agreement with published experimental data. The model was then used to predict the effect of insert number, diameter, height and roughness on critical velocity of manufacturing scale columns.



## 1. Introduction

Chromatography is one of the most essential steps in the downstream processing of a therapeutic. The dependence of the production rate on the separation factor achieved during chromatography is so strong, that even a small improvement in production flow rates can translate into a meaningful gain (Langer, 2009). Continuous increases in cell culture titres will require higher levels of throughput than those currently achievable in downstream processing (Shukla and Thommes, 2010). Chromatography, in particular, is likely to face operational challenges associated with the inability to operate columns having diameters beyond 2 m. Improvements in chromatography operations will be of pivotal importance for the purposes of increasing productivity but most at the same time satisfy the purity specifications required by regulatory agencies.

Chromatography operations are usually developed using laboratory scale columns having diameters less than 3 cm and characterised by aspect ratios (defined as column diameter to bed height) of less than 0.08. The current chromatographic scale-up methodologies suggested in the literature and applied in industry are based on increasing column diameter so as to accommodate the increase in process volume, while maintaining the bed height and superficial flow velocity (Carta and Jungbauer, 2010).

The operational flow rate of a column is commonly evaluated on the basis of the magnitude of the critical velocity, defined as the superficial flow velocity at which the pressure–superficial flow velocity curve rises without limit. The presence of frictional forces between the walls and the resin alleviates the mechanical and hydrodynamic stresses applied on the resin itself. The wall support

* Corresponding author at: The Advanced Centre for Biochemical Engineering, Department of Biochemical Engineering, University College London, Bernard Katz Building, Gordon Street, London WC1H 0AH, UK.
Tel: +44 207 679 9586; fax: +44 207 916 3943.
*E-mail address:* nigelth@ucl.ac.uk (N.J. Titchener-Hooker).

http://dx.doi.org/10.1016/j.ces.2015.02.010

depends mainly on the aspect ratio of the column and it is considered negligible for aspect ratio values larger than 2 (Stickel and Fotopoulos, 2001).

Estimation of the critical velocity of a column is generally conducted through empirical correlations of gravity-settled bed height, column diameter, feed viscosity and compressibility of the chromatographic media used (Stickel and Fotopoulos, 2001; Tran et al., 2007). Additionally, structural mechanics models have been applied to calculate critical velocity values by investigating the stress state in rigid and compressible chromatography resins (Chase and Willis, 1992; Chen et al., 2005; Cherrak et al., 2001; Colby et al., 1996; Hekmat et al., 2013; Keener et al., 2004; McCue et al., 2007; Östergren, 1999). The majority of these models were developed in a two-dimensional coordinate reference system. They describe the pressure–superficial flow velocity behaviour using Darcy's law and treat the resin as a porous material. They can take into account material nonlinearity in the case of compressible resins by expressing the Young's modulus as an empirical function of the particle porosity (Östergren, 1999). The empirical parameters of the Young's modulus equation are best-fitted to independent compression experimental data (McCue et al., 2007).

Many of the resins currently used in industry are made from materials which tend to be compressible and having relatively high porosities in comparison to rigid resins (Chase, 1984). Their compressible nature adds a constraint on the flow rate to which a column can operate, limiting its throughput. Compression of the resin intensifies with an increase in the column aspect ratio as a result of loss of wall support. Manufacturing scale columns may have diameters above 1 m, and hence aspect ratios above 5. Therefore, for a given resin, the operating superficial flow velocity of manufacturing scale columns is necessarily smaller than that of the corresponding laboratory scale columns in order to avoid collapse of the resin due to diminished wall support.

The use of cylindrical inserts of negligible thickness has been initially proposed by Sada et al. (1982) and later on used by Lan et al. (2012) as a way to enhance the level of wall support, allowing higher superficial flow velocities to be applied. Sada et al. (1982) do not provide a mathematical model, which can be used to predict or give some insight on the number of inserts required to increase the critical velocity of packed bed columns of varying size and resin material used. Lan et al. (2012) developed empirical models to describe the effect of the position and the diameter of insert(s) on the critical velocity of a 10 cm diameter column. They conducted acetone pulses experiments, which do not show dispersion or tailing in the acetone pulse curve. Additionally, there was not a significant change in plate number, asymmetry factor or acetone retention time. They achieved up to a 30% increase in critical velocity without affecting significantly the chromatographic efficiency as the number of height equivalent to a theoretical plate (HETP) dropped by less than 10%. Those models have coefficients with no physical representation, as they are of empirical nature. Therefore, they are valid only for the resin type, column dimensions and insert number used.

By contrast, this study uses structural mechanics modelling to describe the effect of inserts on the critical velocity of chromatography columns. The parameters and variables of the model have physical representation. Therefore, they might be used to provide insight in cases where resin material with different mechanical properties and column/inserts with different dimensions are used. Additionally, the volumetric strain of the packed bed column is coupled with the packed bed's elastic modulus and bed void fraction, whereas in previous publications a constant value has been assumed.

Experimental data from Lan et al. (2012) obtained using chromatographic columns of 10 cm diameter supported with inserts were used to calibrate by evaluating the mechanical properties of the resin and the coefficient of friction between the resin and the column wall and verify the structural mechanics models by increasing the number of inserts supporting the column. The model was then used to optimise the diameter and height of the insert, so as to maximise the critical velocity for a given combination of column geometry and resin, allowing higher throughput to be achieved. The verified model provides a thorough understanding of the impact of the inserts on the stress distribution inside the column, and establishes rules for the correct selection of the dimensions of column inserts to be used so as to maximise its operational superficial flow velocity without the need for laboratory-intensive and time-consuming experiments.

## 2. Materials and methods

### 2.1. Experimental setup

An ÄKTApilot™ system (GE Healthcare, Uppsala, Sweden) was used to obtain column pressure–superficial flow velocity relationships and consequently to determine critical velocity values. A pressure transducer (Digitron 2083P, Digitron Communication, Inc., Cambridge, UK) was connected to the inlet of the column so as to obtain more accurate pressure measurements than those the ÄKTApilot system could provide. A BPG 100 column (inner diameter: 10 cm) (GE Healthcare, Uppsala, Sweden) packed with Purabead® 6XL (ProMetic Biosciences Ltd, Cambridge, UK) resin was used in this study. Purabead 6XL is a 6% v/v cross-linked agarose-based resin with no ligands attached. It has an average particle diameter of 90 μm. The physical constants used in the modelling simulations for this type of resin are presented in Table 1.

### 2.2. Inserts

All inserts were purposely made of hollow cylindrical shape made of stainless steel (Fig. 1). Inserts were placed concentrically within the columns and their orientation was secured by stainless steel bars bearing on the column walls to allow precise location of the insert. The insert heights were always marginally less than the height of the packing in the column in order to allow free movement for the top adaptor of the column during column packing. The wall thickness of the inserts was 50 μm. The column was packed with Purabead 6XL resin to 0.10, 0.15 and 0.20 m bed heights. The diameter of the insert was 33%, 50% and 66% of the column diameter and its height was 3/4 of column initial height.

### 2.3. Column packing procedure

Homogenous slurries of resin (in 20% v/v ethanol) were made to a concentration of 70% v/v gravity settled bed slurry volume and used for column packing. Inserts were placed in the column before reverse osmosis (RO) water and then the bead slurry was poured into the column. This achieved homogenous packing of the beads and was reproducible in terms of bed characteristics (axial dispersion and packed height). The resin was left to settle overnight after which the adaptor was lowered to 1 cm above the settled bed. Subsequently, the column was equilibrated using RO water at a flow rate of 10 cm $h^{-1}$ for 40 min.

**Table 1**
Physical constants used in modelling simulations.

| Resin | Mean bead size (μm) | Initial bed void fraction ( ) | Column wall friction coefficient ( ) | Poisson ratio ( ) |
|---|---|---|---|---|
| P6XL | 90 | 0.41 | 0.16 | 0.29 |