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MONITORING OF MULTIPHASE PHARMACEUTICAL PROCESSES USING ELECTRICAL RESISTANCE TOMOGRAPHY

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Recent developments in the use of non-intrusive, electrical measurements to interrogate mixing processes in batch vessels have triggered a joint GSK/Imperial College London project aimed at assessing the applicability of electrical resistance tomography (ERT) to pharmaceutical chemical development. Several vessel/stirrer configurations designed to mimic typical plant reactor geometries were investigated in connection with multiphase processes typical of the pharmaceutical industry. Case studies related to liquid–liquid dispersion and solids suspension in stirred tanks are described and the data obtained are compared with on-line monitoring information as well as computational fluid dynamics modelling results. Overall, very encouraging results were achieved for model and industrial processes. This approach shows promise for on-line control of process mixing performance as well as efficiency evaluation and optimization of several reactor geometries. This allows us to conclude that ERT is a valuable tool for the development of robust active pharmaceutical ingredient (API) manufacturing processes.

Keywords: pharmaceuticals; multiphase mixing; electrical resistance tomography (ERT); CFD; stirred tank reactor; crystallization, phase inversion; retreat curve impeller.

INTRODUCTION

Motivation

Relatively little research has been carried out to evaluate the mixing efficiency of vessels commonly used in the fine chemicals and pharmaceutical industry. The knowledge of the mixing performance of reactors is particularly relevant to the scale-up of multiphase processes, where processing problems such as encrustation, attrition or inadequate mass transfer can be very costly in terms of cycle time or product quality. However, there is now a clear drive from the industry to improve design of processes either by implementing new and continuous technologies or by gaining better understanding of the performance of existing types of stirred tank reactors. This can be observed in the significant development of process analytical technologies over recent years, where continuous monitoring of the chemical aspects of the process through spectroscopic techniques such as UV or NIR is applied. However, in order to fully understand the performance of a process, it is critical to monitor its physical aspects so that the relationship between chemistry and equipment can be fully understood at all scales. The recent and rapid development of non-intrusive electrical measurement techniques such as electrical resistance tomography (ERT) appears to provide a valuable set of tools for the analysis and control of mixing processes. The technology promises to be particularly suited for monitoring multiphase processes and has the potential to provide valuable information for the predictive scale-up of new chemical entities (NCE) into pilot plants, which is considered to be a critical step in the chemical development process.

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Previous Work

Until recently, very little research has been published on the application of electrical tomographic techniques to industrial processes in stirred tanks. The most relevant publication relates to the polymerization of nylon (Dyakowski *et al.*, 1999). However, a significant amount of work has been carried out over the last 10 years on the application of electrical resistance tomography to multiphase processes (West *et al.*, 1999). It must be noted that although results have been compared with data from simplified models such as the Network of Zones (Mann *et al.*, 1997), no detailed evaluation of the tomographic data against known correlations and CFD models has been published. Moreover, literature is scarcely available on mixing in stirred tanks fitted with impeller geometries relevant to the pharmaceutical industry (Bourne *et al.*, 1984; Vershuren *et al.*, 2000; Hattou and Costes, 1997).

Objective

The objective of the current joint project between Imperial College London and GSK is to evaluate the applicability of ERT to the chemical development of active pharmaceutical ingredients (APIs) in stirred tanks. The approach being followed is to gradually increase the complexity of the processes being studied. Our earlier work presented the development of a sensor suitable for the study of pharmaceutical processes at laboratory scale and the application of the technology to a single phase process (Ricard *et al.*, 2003). The present work describes the application of the technology to solid–liquid and liquid–liquid systems in stirred tanks and the use of these data to assess the validity of associated CFD models and correlations.

THEORY

Electrical Resistance Tomography (ERT)

Process tomography involves the use of non-intrusive sensors to acquire two- or three-dimensional images of the internal contents of process vessels, reactors, separators or pipelines and, more recently, the dynamic behaviour of these systems. Several publications contain useful accounts of the historical development of process tomography since the late 1980s (Dickin and Wang, 1996; York, 2001). Very rapid development has followed, especially in the field of electrical tomography and several applications of tomographic techniques to process systems have been published (York, 2001; Williams and Beck, 1995; Williams and Scott, 1995). With the arrival of commercially available tomography systems, the technology has reached a new stage of development, where a more systematic application to industrial processes is taking place. A review of the development of electrical resistance tomography technology and its suitability to fulfil the requirements from the process industry has been presented in our earlier work (Ricard *et al.*, 2003).

The use of ERT to study solid–liquid systems in stirred tanks has been reported in the literature (McKee *et al.*, 1995; West *et al.*, 1999). Several physical phenomena have been observed using ERT in solid–liquid systems, such as settling at the vessel base, accumulation behind baffles, settling on the impeller and the effect of solids addition. Most of the previous work has dealt with model fluids and solids in steady state systems. The solids used are usually electrically non-conducting and their presence in the liquid affects the electrical conductivity measurements when compared to a reference frame taken in the homogeneous liquid. The resolution of the ERT system is not sufficient to provide information about the size and shape of the individual particles, but data on the local volume fraction of solids can be extracted. Bolton *et al.* (2002) presented results using linear sensor on lab and pilot scale and obtained axial solids distribution profiles. Overall, the literature on the application of ERT to solid–liquid systems is concerned with demonstrating proof of concept. Little information on the quantitative validation of ERT data for solid–liquid systems using, e.g., Zwietering's correlation (Zwietering, 1958) for just-suspension speed has been published. No literature has been found on the application of ERT to liquid–liquid systems in stirred tanks.

The variation of the electrical conductivity of a pure liquid with the addition of electrically insulating solid particles has been known and used for many decades. Maxwell's early work (1881) demonstrated that the change in conductivity is proportional to the volume concentration of particles as shown in equation (1). When the concentration of solids C is small, the relative conductivity with respect to the pure fluid is given by

$$K = \frac{2(1 - C)}{2 + C} \tag{1}$$

This relationship and its further development by Bruggeman (1935) have been used extensively for measuring the local concentration of solids suspended in electrolytes. Examples of design, calibration and use of conductivity probes to estimate the local volume fraction of solids can be found in the literature (Stanley *et al.*, 2001; Bujalski *et al.*, 1999). Electrical conductivity measurement has also been applied to the study of crystallization processes, mainly for inorganic salt processes such as ammonium chloride, gypsum, ammonium aluminium sulphate or KDP (potassium dihydrogen diphosphate). The technique was also used to monitor the crystallization of organic compounds such as salicylic acid or citric acid, and to monitor polymorphic changes. Electrical conductivity measurement has recently found success in the pharmaceutical development area and Chatten (cited by Durand-Vidal *et al.*, 1996) has published a review of the applications of electrochemical techniques to the pharmaceutical industry including acid and base titrations of solutions of dissolved tablets.

In the area of liquid–liquid mixing, measurement of conductive and dielectric properties has been widely used for studying and characterizing emulsions for the past 30 years. Robin *et al.* (1994) described the application of electrical conductivity to dairy emulsions and assessed the validity of several theoretical models that described the relationship between electrical conductivity and phase volume fractions of dispersions. A review of the application of conductivity probes to monitor two phase gas–liquid systems can also be found in the literature (Jones, 1983).

Solid–Liquid Mixing

Just-suspension speed

The presence of solids in stirred tanks is extremely common in the process industry and presents one of the main difficulties from a mixing perspective, as they can generate settling, encrustation, shearing/attrition, agglomeration, gelling, mass transfer limitations or drawdown problems. A common processing issue is the suspension of solids denser than the bulk fluid in stirred tanks. Zwietering (1958) defined a widely-acknowledged parameter for the suspension of solids called the just-suspension speed, N_{js}, which is defined as the minimum speed for which no solid particles remain static at the base of the vessel for more than one to two seconds. Further information is available in the literature (Harnby *et al.*, 1992). The Zwietering