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Content and Abstracts

The use of computational fluid dynamics for the study of particle dispersion routes in the filling area of a blow-fill-seal process

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An important issue when producing sterile drugs or medicinal products by aseptic processing with blow-fill-seal technology is to achieve an airborne particle cleanliness of ISO Class 5 for particles ≥0.5 micron for US and EU, and ISO Class 4.8 for particles ≥5.0 micron for EU compliance in the critical area, which includes the filling zone. Most blow-fill-seal machines are

equipped with a filling shroud in the filling area, above the ampoules. The shrouds are often pressurised using either HEPA-filtered air or sterile filtered air. The pressure inside the shroud results in a downwards directed airflow, which creates a cleaner environment around the open ampoules during the filling process than the immediate surroundings in the bowels of the machine. The clean environment within the shroud also provides protection for the filling mandrel and nozzles.
This paper describes the use of computational fluid dynamics to simulate air velocity magnitudes and mass flow rates as a means of better understanding particle dispersion routes in the filling area of a blow-fill-seal process and the impact different parameter settings can have on airborne particle concentrations in the filling area. The results show that the movements of the mandrel, together with its nozzles, is the main cause of particles present in the filling shroud during the manufacturing process. The computational fluid dynamics results suggest that particle concentrations can be reduced by changing the mandrel velocity and the mandrel shape. It should be noted that results presented in this paper are limited to one type of BFS machine.

Key words: computational fluid dynamics, CFD, shroud, airborne particles, blow-fill-seal

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Reading the runes: demystification of disposable glove legislation

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The use of disposable gloves in the general working environment is widespread. Indeed they are such a big part of our working lives that glove usage in the US has dramatically increased from less than 1 billion to over a 20 billion. We tend to use disposable gloves for either process protection from human-borne contamination or for personal protection and often for both reasons. However as safety in the occupational environment becomes an increasing concern, do we really understand what level of protection we are getting?

Key words: Disposable gloves, latex gloves, nitrile gloves, Medical Device Directive, Personal Protective Equipment.

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Stabilisation of doxorubicin hydrochloride using sugar-phosphate glass composites prepared by vacuum foam drying

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The objective of the present work was to investigate the use of vacuum foam dried lactose-phosphate composites for the stabilisation of doxorubicin hydrochloride at ambient temperature and to compare the use of sodium salts of mono and dibasic phosphates. Vacuum foam dried systems of doxorubicin hydrochloride with varying concentrations of lactose, phosphates and polyvinyl pyrrolidone were prepared. The finished products were evaluated for processing and storage stability using foam characteristics, residual moisture content, reconstitution time, drug-excipient interactions and percent drug content. The physical state of products was studied using X-ray powder diffraction, light microscopy, Fourier transform infrared spectroscopy and differential scanning calorimetry. The effects of pH, lactose, phosphates and polyvinyl pyrrolidone K30 on foamability and foam strength were studied. Studies with lactose showed that it formed an amorphous glass under the experimental conditions. Vacuum foam dried products with 10% w/v lactose and 1.5% w/v sodium dihydrogen phosphate showed an increase in glass transition temperature due to an increase in the sugar-phosphate interaction. Monobasic phosphates showed superior stability to dibasic phosphates. The dried foamy products stored at 2–8°C and 25°C displayed better stability compared to products stored at higher temperature. This was attributed to increased molecular aggregation. Storage below the glass transition temperature is important to maintain the rigid-glass structure and hence stability of such products.

Key words: Stabilisation, vacuum foam drying, doxorubicin hydrochloride, lactose, phosphates.

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Formulation and evaluation of sustained release suppositories of ondansetron in hydrophilic and lipophilic bases

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The purpose of this study was to develop a sustained release suppository of ondansetron and also to study the effect of the water swellable polymer hydroxylpropylmethyl cellulose (HPMC K4M) on the in vitro release of ondansetron from suppositories. Suppositories were prepared by using Suppocire AM, polyethylene glycol (PEG) 4000 and PEG mixture (PEG 1500: PEG 4000) as lipophilic and hydrophilic bases. Suppositories containing 16mg of ondansetron were prepared by the fusion method. Weight variation, content uniformity, breaking (hardness), melting point, disintegration and liquefaction time were conducted on these formulations. In vitro release test was carried out according to the USP XXII basket method. The results demonstrate an 82% release of ondansetron from Suppocire AM, while 90-98% release of ondansetron from PEG base was seen in conventional suppositories within 90min. On the other hand, HPMC maintained the ondansetron release from suppositories for up to 12h. It was shown from kinetic assessment of in vitro release data, that the suppositories containing PEG 4000, and the PEG mixture and Suppocire AM based suppositories followed predominantly diffusion control. A stability study indicates that the shelf storage does not change the amount

of drug released from each of the tested formulations. In vitro ondansetron release was sustained by the addition of HPMC K4M. Ondansetron was stable in both lipophilic and hydrophilic suppositories with HPMC, and the physicochemical characteristics and the drug content of the suppositories were satisfactory for practical use.

Key words: ondansetron, suppository, sustained release, hydroxylpropylmethyl cellulose, Suppocire AM, polyethylene glycol.

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Content and Abstracts

Improving scalability and comparability by using single-use bioreactors for large-scale manufacturing

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Although single-use bioreactors are widely accepted for R&D and seed train applications, their use in real production environments has stayed very limited until now. However, with the recent introduction of single-use bioreactors with a classical design this is now changing. These new bioreactors reduce the need for additional optimisation when moving away from stainless steel and simplify the upscaling process. Therefore it is expected that these single-use bioreactors will more and more find their way into large-scale production applications, allowing for total single-use solutions throughout the complete process.

Key words: Single-use bioreactors, classical design, scale up, single-use sensors, process control, aeration, mixing requirements

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Development of intravenously injectable solution of carvedilol using a combination of pH adjustment and micellization.

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Purpose: The objective of the work was to enhance aqueous solubility of carvedilol to prepare an intravenously injectable solution.

Method: Solubilisation techniques included pH adjustment and use of a micelle forming block polymeric surfactant. The final solution was subjected to various physicochemical and preclinical in vivo tests to evaluate its suitability for intravenous injection.

Result: pH adjustment was found to be more effective than the surfactant to increase the solubility of carvedilol. However, complete solubilisation was achieved with a combination of the two techniques. The drug solution withstood extreme dilution without any sign of precipitation. Addition of drug was found to increase zeta potential and hydrodynamic zeta size. In vivo administration did not show any acute adverse event.

Conclusion: An intravenously injectable solution of carvedilol was developed and characterised. The formulation will facilitate achieving quick onset of action of carvedilol in acute cardiovascular complications.

Key words: Disposable gloves, latex gloves, nitrile gloves, Medical Device Directive, Personal Protective Equipment.

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Design of HEPA-filter units in order to prevent airborne contamination of autoclaves and freeze dryers when doors are open

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In pharmaceutical manufacturing autoclaves and freeze dryers generally cause temperature differences relative to the ambient air when doors are open during loading and unloading. This causes flows of room air through the openings creating contamination risks. To minimise these risks, high-efficiency particulate air (HEPA) filter units are installed above the openings to provide clean air as protection. In this paper design criteria for needed air volume flows through HEPA-filters are discussed and results from a case study describing risk situations with and without airflows through a HEPA-filter are presented.

Key words: Freeze dryer, autoclave, aseptic loading/unloading, temperature difference, airborne contamination

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Hot-melt extrusion technology: optimizing drug delivery

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Hot-melt extrusion (HME) technology was first utilised predominantly in the plastic industry and to a lesser extent in the food industry since the 1930s. The many advantages of HME over conventional solid dosage form manufacturing have piqued the interest of the pharmaceutical industry and academia as a novel drug delivery technology. This innovative technology has been shown to be extremely robust and a viable method of producing many different drug delivery systems, including implantable reservoirs, pellets, films, capsules and tablets. Moreover, the possibility of forming solid dispersions offering improved bioavailability renders HME an excellent alternative to other conventionally employed techniques. This article aims to provide, an overview of the technique, a basic guide to extrusion equipment and process technology, the fundamental principles of operation and to discuss the most recent applications of HME within the field of drug delivery.

Key words: Hot-melt extrusion; extruder; pharmaceutical applications; solid dispersions; dosage forms.

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Content and Abstracts

Contamination of cleanrooms by people

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It is widely accepted that the activities of people in cleanrooms are a, if not the, major source of particulate contamination, mainly in the form of large numbers of shed skin cells, and that that these particles carry correspondingly large, or even larger, numbers of micro-organisms. The experiment described was conducted to test this belief by measuring contamination levels caused by people placed in a normally operational pharmaceutical cleanroom, rather than by drawing conclusions from extrapolated laboratory test data.

Key words: cleanroom, people, skin cells, viable particles, nonviable particles, micro-organisms, garments, clothing, activity, settle plates, air samplers

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A review of ionic liquids in pharmaceutical microbiology: antimicrobial and antibiofilm reagents

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Ionic liquids research has experienced unprecedented growth in the past two decades, primarily in the field of 'green chemistry' and the replacement of volatile organic compounds in the chemical industry. The ability to tune the physical, chemical and biological characteristics of ionic liquids via independent modification of the cation or anion introduces flexibility in the design of functional reagents or 'designer solvents'. Whilst much research has concentrated on chemical applications, biological toxicity has become increasingly scrutinised. Recently, the antimicrobial and antibiofilm activities of ionic liquids have been described, opening the possibility that ionic liquids may be specifically tailored for use as antimicrobials in a range of applications. The use of ionic liquids as antimicrobial agents is reviewed here.

Key words: Ionic liquids, antimicrobial, biofilm, disinfectant.

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Particle concentrations in small volume parenterals produced by aseptic

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When producing sterile drugs or medicinal products by aseptic processing with blow-fill-seal (BFS) technology it is important to achieve an airborne particle cleanliness of ISO Class 5 for particles ≥0.5 micron for US and EU, and ISO Class 4.8 for particles ≥5.0 micron for EU compliance in the critical area, which includes the filling zone. Most BFS machines are equipped with a filling shroud in the filling area, above the ampoules. The shrouds are often pressurised using either HEPA-filtered air or sterile filtered air. This results in a downwards directed airflow, which creates a cleaner environment around the open ampoules during the filling process than the immediate surroundings within the machine region. The clean environment within the shroud also provides protection for the filling mandrel and nozzles. BFS machines which use hot knives for the cutting of plastic parisons are known to generate significant amount of particles and the regulatory requirements can sometimes be difficult to fulfil. These requirements do not take into account the short exposure time for small volume parenterals produced with BFS.

This paper describes an experimental study performed on one BFS machine in order to increase the understanding of the relationship between airborne particle concentration and particle concentrations in filled small volume parenterals. The airborne particle concentration in the critical area of the BFS process was increased 1,000 fold (particles ≥0.5 micron) during filling with NaCl fluid. Following the particles challenge, samples of filled ampoules were

analysed through light obscuration particle count. The result showed no increase of particles in the filled ampoules. Likely explanations to the result are the short exposure time and small exposure area.

Key words: airborne particles, blow-fill-seal, aseptic, small volume parenteral

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In vivo evaluation of ketorolac sustained release pellets using a new HPLC method

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The objective of the study was to develop a simple, rapid and specific method for analysis of ketorolac trometamol (KT) in plasma and apply it for the pharmacokinetic evaluation of experimental sustained release pellets against a commercial tablet containing KT. In vivo availability of KT following administration of a sustained release pellet formulation against a reference tablet was carried out in six healthy male volunteers aged 20-26 years and weighing 60-69kg.

Higher plasma concentrations were observed with the sustained release pellets compared with the tablets. Based on the area under the plasma concentration-time curve to infinity (AUC0-inf), the calculated % bioavailability of the pellets relative to tablets was 104%. The pellets showed higher peak plasma concentrations, which exceeded the reported minimum effective concentration of KT for 8h; compared with only 2h with tablets.

The proposed HPLC method is suitable for bioavailability evaluation of KT in dosage forms with a high degree of specificity, accuracy, precision and using small plasma samples. The prepared pellets possess several advantages over the tablets, which will be of value in increasing drug efficacy and reducing frequency and side effects, as well as improving patient compliance.

Key words: Ketorolac trometamol, HPLC, relative bioavailability, sustained-release pellets, reference tablet, human volunteers.

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Content and Abstracts

Pharmaceutical risk management: reflections on origins and the current situation

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Risk management is a concept as old as humankind, but until recently it hadn't been fully implemented in terms of pharmaceutical quality assurance. As often happens with self-evident concepts, a risk management approach has to deal with many more implementation problems than could be imagined beforehand. Practical risk management origins and the current implementation situation are reviewed and discussed.

Key words: Risk analysis, risk assessment, validation

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Development of local, mucoadhesive, sustained release patches of tetracycline hydrochloride for treatment of mouth infections: a preliminary in vitro study

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The aim of this study was to develop tetracycline hydrochloride sustained drug delivery system for local treatment of mouth infections, and to demonstrate the feasibility of xanthan gum as a film forming material that can be used in buccal drug delivery systems. The bilayered patches were prepared using ethyl cellulose as a backing layer, and xanthan gum as a matrix mucoadhesive layer. The patches were prepared by solvent-casting method with different loading amounts. In vitro drug release was performed using Franz-diffusion cells. Antibacterial activity was assessed for all prepared patches using disc-diffusion method against Escherichia coli, Bacillus cereus, Staphylococcus aureus and Bacillus bronchisepti. Ex vivo mucoadhesive force, swelling studies, physical characteristics, and Fourier transform infra-red spectroscopy were performed for all the patches. The sustained action was achieved for 8h, with effective microbial activity against the tested microbes. The polymer reserved acceptable swelling with average value 400% for water uptake. The mucoadhesion force was 50*103 dyne/cm2 and it was adhesive for more than 8h. The addition of selected loading amounts of tetracycline hydrochloride did not result in a change in swelling or mucoadhesive properties. The patches were smooth, elegant in appearance, uniform in thickness, weight, drug content, and possessed good folding endurance (>200). In this study, preparation of sustained release buccal mucoadhesive patches was obtained. This study illustrated the feasibility of xanthan gum as a mucoadhesive film forming polymer. The patches were elastic and easy to prepare and can be used as a model for buccal drug delivery system of any water soluble drug.

Key words: buccal drug delivery, water uptake, antibacterial, tetracycline hydrochloride, FTIR, mucoadhesion.

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Selection of active air samplers

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Viable microbiological environmental monitoring is a key aspect of any sterility assurance programme in order to assess the number of viable micro-organisms present. A viable environmental monitoring programme requires the use of a range of different techniques. These can be divided into air samples, surface samples and personnel samples. Air samples include both passive (settle plates) and active (using a sampling device).1 Microbial air samplers are used to collect a predetermined volume of air and operate in a way to remove any micro-organisms and to capture the micro-organisms onto an agar-based growth medium. Once the sample has been collected and the medium incubated, the results are typically expressed in colony forming units per cubic meter (cfu/m3).

One of the more difficult choices facing an organization is which type of active air sampler to select. The use of active air samplers is highlighted by the FDA (in the 2004 Guide to Aseptic Filling) and in the international cleanroom standard for biocontamination control: ISO14698-1, as being of fundamental importance to any environmental monitoring regimen. Active air samplers allow the number of micro-organisms in a given volume of air or measured over a set period of time to be captured onto a microbiological culture medium and then to be enumerated. Micro-organisms are not evenly distributed in air and several factors such as moisture, temperature, electrostatic charge, light, air movement, and so on, influence the distribution2. There are many variations in the type of active air sampler and in the efficiency of different models. No single model or type has universal acceptance and each model has strengths and weaknesses. This paper details some of the variations associated with active air sampling, with an aim of guiding the reader into making an informed choice.

Key words: Active air sampler, volumetric air sampler, bioburden, GMP, air flow, particle size, environmental monitoring

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Formulation and evaluation of gastroretentive drug delivery of verapamil hydrochloride

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The objective of the present research work was to formulate and evaluate floating tablets of verapamil hydrochloride using direct compression technology. Verapamil hydrochloride has pH dependent solubility. It is mainly soluble in gastric fluid pH as compared to intestinal fluid pH. Various grades of hydrophilic and hydrophobic polymers such as HPMC K 15 M, HPMC K 100 M, HPMC K 100 LV and carbopol 971 P were used in the formulation of a floating drug delivery system. Carbopol was capable of sustained delivery of verapamil hydrochloride for a longer period with increased bioavailability. Incorporation of sodium bicarbonate and citric

acid as a gas generating agent into the tablet matrix resulted in floating over simulated gastric fluid for more than 12 hours.

In floating sustained release tablets, crosspovidone was added as a drug release modifier. Tablets were prepared by physical blending of verapamil hydrochloride and polymers in varying ratio. The formulation was optimized on the basis of in vitro floating behaviour and in vitro drug release. Drug release rate kinetics were assessed by fitting the release data into dissolution kinetic study models (Zero order, First order, Higuchi and Korsmeyer-Peppas).

The in vitro dissolution profile showed an anomalous type of diffusion.

Key words: Verapamil hydrochloride, floating dosages form, in vitro evaluation, release kinetics.

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