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Dry powders for oral inhalation free of lactose carrier particles ☆

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ABSTRACT

Dry powder inhaler (DPI) products have traditionally comprised a simple formulation of micronised drug mixed with a carrier excipient, typically lactose monohydrate. The presence of the carrier is aimed at overcoming issues of poor flowability and dispersibility, associated with the cohesive nature of small, micronised active pharmaceutical ingredient (API) particles. Both the powder blend and the DPI device must be carefully designed so as to ensure detachment of the micronised drug from the carrier excipient on inhalation.

Over the last two decades there has been a significant body of research undertaken on the design of carrier-free formulations for DPI products. Many of these formulations are based on sophisticated particle engineering techniques; a common aim in formulation design of carrier-free products being to reduce the intrinsic cohesion of the particles, while maximising dispersion and delivery from the inhaler. In tandem with the development of alternative formulations has been the development of devices designed to ensure the efficient delivery and dispersion of carrier-free powder on inhalation. In this review we examine approaches to both the powder formulation and inhaler design for carrier-free DPI products.

Contents

Abbreviations: API, active pharmaceutical ingredient; AUC, area under the curve; BSA, bovine serum albumin; C_{max}, peak concentration; COPD, chronic obstructive pulmonary disease; DPI, dry powder inhaler; DPPC, dipalmitoylphosphatidylcholine; ED, emitted dose; EMA, European Medicines Agency; EMEA, European Medicines Evaluation Agency; FDA, Food and Drug Administration; FDKP, fumaryl diketopiperazine; FPF, fine particle fraction; G-CSF/M, granulocyte-colony stimulating factor/mannitol; HPβCD, hydroxypropyl-beta-cyclodetrin; LPNP, large porous nanoparticulate; LPP, large porous particle; MCT, microstructured carrier tape; MMAD, mass median aerodynamic diameter; NIMs, nano-in-microparticles; NP, nanoparticle; NPMPs, nanoporous/nanoparticulate microparticles; PEG, polyethylene glycol; PLGA, poly(lactic-co-glycolic) acid; SEM, scanning electron microscopy; $scCO_2$, supercritical carbon dioxide; SPION, superparamagnetic iron-oxide nanoparticle; TEM, transmission electron microscopy; t_{max}, peak time; TSI, tobramycin solution for inhalation.

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1 . Introduction

The efficient delivery of an active pharmaceutical ingredient (API) to the respiratory tract from a dry powder inhaler (DPI) depends on four interdependent parameters — the formulation, the metering system (capsule, multi-unit dose and reservoir dose containment elements), the inhaler device and the patient's inhalation technique. In order to achieve good penetration into the pulmonary regions it is generally accepted that particles should have an aerodynamic particle size between 1 and 5 μm. However, particles of this low micron size have a high surface free energy, with a tendency to stick together (*via* cohesive forces) or to any surfaces they encounter (*via* adhesive forces), in an attempt to reduce the surface energy. Such small particles are thus very cohesive or "sticky" and exhibit poor flowability and aerosolisation performance, with a propensity to be retained in the inhaler if used alone. For this reason, in order to improve flowability and dispersion of API particles, the micronised API is usually mixed with an inert carrier or "flow aid" comprising a population of coarse particles (50 to 100 μm in diameter) [1].

Lactose monohydrate is the most commonly used excipient carrier material in DPI formulations. Mixtures of the lactose with API are often called ordered or interactive mixtures, which are easier to handle during the manufacturing processes than micronised API alone. The use of a carrier excipient makes manipulation of small drug doses possible. A typical drug-to-carrier ratio is 1:67.5 [2,3]. The API particles should loosely adhere to the carrrier particles and during inhalation in the turbulent airstream which is created, the API particles detach from the carrier particles and are made available for deposition into the lungs. The larger carrier impacts in the mouth and at the back of the throat and is swallowed. The carrier excipient also provides bulk to the formulation, which improves the handling, dispensing, and metering of the drug, which is of particular importance for low dose formulations such as steroids (typical dose per actuation: 50 μg to 500 μg).

In order to ensure efficient delivery of API, it is critical that adhesive forces between the API and carrier are not so strong that detachment from the carrier is prevented. The balance between adhesive and cohesive forces should be adjusted to ensure sufficient adhesion between drug and carrier so as to provide a stable formulation (homogeneous blend with good content uniformity) but with adequate separation of API from carrier on inhalation. It has been recognised that the efficiency of a powder formulation is highly dependent on the lactose quality, lactose source, particle size and particle size distribution, fine-lactose content, and the inhalation flow rate and dispersion capacity of the respective DPI device [4].

The development of carrier-free dry powder inhaler formulations has the potential to overcome issues associated with lactose (or other carrier) as a critical component of the formulation. Problems of blend uniformity are avoided (for single API formulations) and the aerosolisation properties of the formulation will depend on the characteristics of the API particles or API-containing particles, together with DPI inhaler performance and the patient's inhalation technique.

Additionally, the absence or limited amount of excipient included in carrier-free formulations permits the inhaled powder mass to be limited, and makes the delivery of high dose actives (*e.g.* antibiotics) to the lungs possible. Over the last two decades significant efforts have been invested in the design of carrier-free dry powder inhaler formulations, based on sophisticated particle engineering techniques, together with inhalers suitable for delivering such carrier-free powders efficiently to the patient. A common aim in developing carrier-free products is to reduce the intrinsic cohesion of the particles, while maximising dispersion and delivery from the inhaler.

This review will present the particle technologies on which carrier-free DPI formulations are based, including platform technologies which have resulted in commercial products. Also presented is a short review of marketed dry powder inhalers (DPIs) which have been developed to deliver these formulations, as well as inhaler devices currently in development.

2 . Carrier-free formulations

2.1. Spheroids

Spheroids (soft aggregates) are manufactured by the controlled agglomeration (spheronisation) of micronised particles. Spheroids have large particle sizes (approximately 0.5 mm in diameter) and thus have appropriate flow properties, significantly better than micronised material, and exhibit little static charging during handling and operating [5]. Commercially they are used with the Turbohaler® device (see Section 4 below) and loaded as spheroids into the inhaler, however they break up into individual, primary particles upon inspiration. It has been reported that the main drawback of such systems containing soft pellets is high variability in the emitted dose, as high as 15% in terms of a total relative standard deviation [6].

Controlled agglomeration is also employed in Asmanex® Twisthaler® and the particles are formulated as free-flowing crystalline agglomerates containing mometasone furoate (the drug) and anhydrous lactose (as a binder) [7].

Edwards and Chambers [8] have presented clinical trial studies comparing the clinical efficacy and asthma patient acceptability of two inhalable preparations of sodium cromoglycate, one containing a blend of the drug (20 mg) and lactose and the other comprising a lactose-free pelletised formulation of sodium cromoglycate (20 mg). It has been found that no clinically significant differences were observed between the two formulations after three months moreover, after the period of six months use the carrier-free system was revealed to have a higher proportion of "very effective" clinical scores compared with the carrier-based formulation. No details of the production method for spheronised sodium cromoglycate were disclosed by the authors.

Vidgren et al. [9] compared *in vitro* deposition and clinical efficacy of two DPI formulations, Blacil® – composed of a mixture of micronised sodium cromoglycate and lactose as carrier and Lomudal® – comprised of pelletised drug. A larger fine particle fraction was achieved in the cascade impactor *in vitro* from Blacil® compared to Lomundal®, however the preparations were found to be equally effective *in vivo*.

2.2. Coated particles

Aerosolisation of inhalable particles can be improved by applying an outer coat formed by lipids or aminoacids using either spray drying, physical vapour deposition or aerosol flow reactor methods.

Pilcer et al. [10] developed and evaluated the physicochemical and aerodynamic characteristics of a lipid-coated dry powder formulation of tobramycin for the treatment of cystic fibrosis. The particles were prepared by spray drying solid particles of tobramycin suspended in a lipid (cholesterol, phospholipon 90H or hydrogenated soy lecithin) solution made with isopropanol. Particle size distributions of the spray dried powders were narrow and monomodal with more than 90% of the particles having a diameter of less than 2.8 μm. The mass median aerodynamic diameters (MMADs) were less than 1.3 and 3.2 μm, with the fine particle fraction (FPF) varying between 50.5 and 68.3%. Evaluation of the influence of the lipid content, which was either 2, 5, or 10% w/w lipids, showed that deposition of only 5% w/w lipids on tobramycin particles was sufficient to improve particle dispersion properties during inhalation. Lipid coating also resulted in a reduced agglomeration tendency of the particles.

Raula et al. [11] studied aerosolisation behaviour of carrier-free L-leucine coated salbutamol sulphate powders. The amino acid coating was applied by physical vapour deposition, in the gas phase, on the spherical surfaces of the drug particles, which were made by aerosol flow reactor. In the aerosol flow reactor method, droplets are first generated by ultrasonic nebulisation, followed by drying of droplets in a stream of dry nitrogen gas in a tubular reactor. Deposition of the excipient resulted in the formation of pointy crystalline asperities and their sizes and surface density (coverage) increased with an increasing content of L-leucine in the gas phase. The FPFs of the coated powders ranged from 42 to 47%, which was 3–4 times higher than FPFs measured for the micronised powder. The emitted doses (EDs) and FPFs of the powders comprising the coated particles decreased as the surface roughness increased. Further studies by Raula et al. [12] showed that the powder emission from the device was primarily affected by the morphology and surface roughness (asperity size and density) of the particles but not by dispersive surface energies.

The preparation of coated particles involving several production steps, such as those used by Pilcer et al. [10] and Raula et al. [11], might not be advantageous for industrial production. Therefore a coated particle technology, based on a one-step process of microparticle formation from drug/L-leucine liquid solutions, is available commercially from a company called Teicos based in Helsinki, Finland. This patented method involves the production of surface modified particles in continuous or batch aerosol reactors [13]. A number of APIs have been shown to be successfully formulated, including salbutamol sulphate, nicotine tartrate, fludrocortisone and growth hormone, but no commercial product is, as yet, available.

Coating with L-leucine was also employed in the preparation of spray dried, carrier-free composite formulations for inhalation containing budesonide and salbutamol sulphate to facilitate simultaneous release of the drugs and to improve dissolution of poorly soluble budesonide [14]. Wet milling was first used to manufacture a nanosuspension of budesonide, which was then added to an aqueous solution containing dissolved salbutamol sulphate, mannitol and L-leucine and processed by aerosol flow reactor (the same method as that used by Raula et al. [11]) into microparticles. Very good aerosolisation performance of the powders, due to the presence of the L-leucine coating, was measured with FPFs reaching ~ 50%. The time for full dissolution of budesonide nanocrystals from the microparticles was approximately 20 min and the same dissolution rates for both drugs were obtained.

Mixed solvent (water/ethanol) systems, at near-azeotropic co-solvent ratios were used to prepare budesonide/L-leucine microparticles by spray drying [15]. Similarly as for the formulations containing hydrophilic drugs [11,12], the surface of the particles was enriched with the excipient. The powders had low densities and their dispersibility and manufacturability properties were seen to be improved in comparison to powders made of budesonide alone. FPFs obtained when a passive DPI was used for aerolisation exceeded 80% and the MMADs were between 2 and 3 μm.

Hoe et al. [16] demonstrated that L-leucine may be substituted with D-leucine without adversely affecting aerosol performance. while introducing another advantage of such spray dried particles in terms of disrupting *Pseudomonas aeruginosa* biofilm growth due to the presence of D-amino acids. Treatment of biofilms with D-amino acids has been found to cause the release of amyloid fibres holding cells together and disassembly of the biofilm [17]. The powders would have a potential application in non-antibiotic antipseudomonal therapy especially in lung infections that are insensitive to antibiotic therapy in cystic fibrosis patients. No differences in microstructure of particles containing L- and D-leucine by Raman spectroscopy were observed and it was concluded that D-leucine, similar to the L-form, behaves as a dispersibility agent.

Feng et al. [18] carried out studies on mechanistic models of spray drying and particle formation processes of L-leucine and trehalose mixtures aimed at elucidating the formation mechanism of L-leucine microparticles and to answer the question as to why this amino acid is very effective at enhancing dispersibility of microparticles. Feng's work has shown that the morphology of spray dried microparticles changed from solid spheres with corrugated surfaces (10-15% mass fraction of L-Leucine) to hollow, thin-walled particles (the most prevalent morphology type for L-leucine mass fractions $\geq$25%) as the leucine mass fraction increased. Also, a correlation of the morphological change and bulk density with the degree of crystallinity of particles was found, implying that the mechanism for the formation of thin shells/thin-walled low density particles is based on crystallisation of the amino acid. The authors concluded that L-leucine crystallinity may be a predictor of particle dispersibility when this excipient is used as a dispersibility agent. The efficacy of L-leucine as a dispersibility enhancer included in spray dried particles has been attributed to its very quick precipitation/crystallisation at the surface of the evaporating droplet, which results in the creation of a shell enriched in this amino acid, while the drug component is contained in the interior of the particle [18,27]. However, optimisation of both the formulation and the spray drying process, is required to achieve early solidification of L-leucine and formation of the hydrophobic and crystalline-in-nature shell that is able to reduce interparticulate forces and hence improve dispersion of particles [15,18].

2.2.1 . Coating by mechanofusion

Another method of improving aerolisation of inhalable drug particles is to apply a mechanical dry coating process. This process is also

termed "mechanofusion" and its application in the design of a dry powder inhaler was demonstrated for the first time by Kawashima et al. [19]. Light anhydrous silicic acid (Aerosil® 200) was employed as a glidant to coat surfaces of micronized pranlukast hydrate, a selective active leukotriene antagonist for bronchial asthma. The excipient was used at 2, 5 and 10% w/w concentrations and two types of mixing approaches were used: premixing followed by further mixing in a manually operated mortar (PM) and a high speed elliptical-rotor-type mixer (Theta-Composer®, TC). Respirable fractions (obtained with a twin impinger apparatus) ranged between 43 and 63% for the PM formulations, 73–79% for the TC systems, while that for the original powder was only approximately 36%. Overall, the inhalation behaviour, as evaluated by the coefficient of inhalation efficiency (the geometric mean of the drug % emitted from the device and % delivered in respirable fraction in the twin impinger) was 48% and 67% for the PM and TC samples, respectively, at 10% level of Aerosil®. This improvement in aerolisation behaviour was attributed to the surface modification of pranlukast, that decreased the cohesive forces between the particles [19].

However, as concerns about the safety of silicic acid used in inhalation products arose, the mechanofusion approach was used to modify the drug particles with magnesium stearate, which is considered to be safe when administered by inhalation [20]. Zhou and co-workers [20] investigated aerolisation properties of three model powdered materials: salbutamol sulphate, salmeterol xinafoate and triamcinolone acetonide mechanofused with 5% w/w magnesium stearate. Two mechanofusion systems: the AMS-Minimechanofusion system with either a Nobilta or Nanocular process module, manufactured by Hosokawa Micron Corporation (Osaka, Japan), were tested. Significant improvements in the aerolisation behaviour (reflected in an increase in respirable fractions as measured by the twin impinger) were noted for all powders subjected to mechanofusion, with the greatest rise in respirable fractions (nearly a two-fold increase) observed for triamcinolone acetonide [20]. An extension of this study was recently published by Zhou et al. [21], where intensive mechanical dry coating of salbutamol sulphate by magnesium stearate was performed using the Nobilta device and the properties of the treated powder were compared to those of a sample made by traditional blending. It was found that 2% w/w of the excipient resulted in the optimum performance in terms of de-agglomeration behaviour, the emitted dose and the fine particle dose of the mechanofused powder, while the traditionally mixed salbutamol sulphate with 2% magnesium stearate was comparable to the untreated powder [21].

Stank and Steckel [22] blended micronised salbutamol sulphate with different concentrations of magnesium stearate or glycerol monostearate followed by co-milling with an air jet mill. The dispersive surface energy of salbutamol sulphate was lowered and the energy distribution was more homogenous for co-milled samples compared to samples which were just blended in a Turbula™ blender.

2.3. Spray dried particles

Spray drying is a widely used method for manufacturing inhalable particulates. Careful design and control of the process can result in particles with wrinkled, spherical or porous morphologies [23–31]. The main advantage of the spray drying process is the ability to manipulate and control a variety of parameters such as solvent composition, solute concentration, solution and gas feed rate, temperature and relative humidity, droplet size, *etc.*, which allows optimisation of particle characteristics such as size, morphology and density, in addition to macroscopic powder properties such as bulk density, flowability and dispersibility [25,32]. One of the main challenges associated with the process is the fact that most materials undergo amorphisation upon spray drying which can become a stability issue [25,32]. Processing of macromolecules by spray drying also presents challenges due to potential for degradation as a result of factors such as thermal stress during droplet drying, high shear stress in the nozzle and also because of peptide/protein adsorption at the greatly expanded liquid/air interface of the spray solution.

2.3.1. Wrinkled particles

French et al. [23] studied the emission, deaggregation and *in vitro* deposition of spray dried (from aqueous solution) mannitol-based particles with and without PEG 8000 carrier from a Spinhaler®. The powders comprising recombinant human granulocyte-colony stimulating factor/mannitol (G-CSF/M) exhibited improved dispersion, better deaggregation and increased deposition in the model lung than those containing only mannitol. The superior performance of G-CSF/M powders was attributed to lower interparticulate cohesive forces between particles originating from surface indentations and lower bulk densities. Carrier particles enhanced total powder emission, but in many cases reduced the amount of the powder containing the protein compared to formulations consisting of G-CSF/M alone. The authors concluded that the use of carrier particles was not considered as necessary.

A comparison of dispersion performance of smooth spherical and non-porous corrugated particles composed of bovine serum albumin (BSA), both prepared by spray drying, was presented by Chew and Chan [24], however an earlier paper by Maa et al. [25] first describes the production of spray dried BSA wrinkled particles. The work of Chew and Chan [24] focussed on the effect of particle surface morphology on aerosolisation of BSA powders. The fine particle fractions of the powder comprising corrugated particles (approximately 50%) were significantly higher than those of the spherical particles using both DPI devices (Rotahaler® and Dinkihaler®). Also, the degree of powder retention in the capsule and device was lower for the corrugated particles. Less dependence of fine particle fraction on flow rate was also observed for the corrugated particles. The better aerosolisation performance of the wrinkled particles was explained by their lower true area of contact resulting from surface asperities.

Lechuga-Ballestros et al. [26] investigated the suitability of trileucine (L-Leucyl–L-Leucyl–L-Leucine) as a functional excipient in inhalable powders. It was seen that the addition of small amounts of trileucine to formulations (microparticulate spray dried powders obtained from a solution containing dissolved drug and the tripeptide) resulted in stable dry powders with improved inhalation properties. A range of active substances was studied, including antibiotics, asthma drugs (salbutamol sulphate and sodium cromoglycate) and peptide hormones (salmon calcitonin and human growth hormone). The particles had corrugated morphologies. Although it was observed that water soluble molecules tended to produce less corrugated and more spherical particles, all powders had low cohesiveness. For instance, netilmicin sulphate and gentamicin sulphate were seen to form smooth spheres with some dimples when spray dried on their own, however when trileucine was added to the mix, particles started to resemble those of trileucine particles, with high rugosity. A significant increase in the emitted dose and fine particle fraction was evident even at low trileucine concentrations (2% mass content in the formulation). The surface of particles was enriched in trileucine as seen in a decrease in the surface energy, correlating with the *in vitro* aerosol performance. The mechanism by which this excipient was yielded the wrinkled, low density particles was further elucidated by Vehring et al. [27], who stated that the corrugated morphology was due to its low solubility of trileucine leading to phase separation and subsequent surface accumulation.

2.3.2. Spray dried spheres

Vidgrén et al. [28] spray dried sodium cromoglycate from water/ethanol solutions, producing spherical, but partially shrunken particles. The physical properties and *in vitro* inhalation behaviour of mechanically micronised and spray dried sodium cromoglycate particles were compared and it was reported that the spray dried particles were smaller, mainly in the range of 1–5 μm, with improved lung deposition as evaluated from impaction studies.

Another example of a carrier-free formulation of spray dried powder consisting of spherically shaped particles suitable for inhalation is the work of Chawla et al. [29] on salbutamol sulphate. In this case, a statistical factorial design was employed to investigate the effect of spray drying parameters on the particle size and production yield. The optimised batch had a median diameter of 4.5 μm (by laser diffraction) and a mass median aerodynamic diameter of 9.7 μm (by cascade impaction). The spray dried material was seen to perform as well as the micronised salbutamol sulphate.

Steckel et al. [30] prepared sodium cromoglicate in a respirable particle size, using an *in-situ*-micronisation controlled crystallisation technique followed by spray drying and compared these particles to the commercial dry powder formulation, Intal®. The spray dried microparticles were spherical and non-porous, but with clearly visible asperities (*i.e.* non-smooth). Delivery of these engineered particles *via* the Spinhaler® device at a flow rate of 100 l/min resulted in a measured fine particle fraction of 45.5%, a statistically significant increase in the fine particle fraction compared to the commercial product (14.5%). An enhanced aerosolisation performance of the spray dried product was also observed when using another DPI device, the FlowCaps®.

Tajber et al. [31] co-spray dried budesonide and formoterol fumarate (weight ratio of 100:6) into smooth, spherical particles with the intention of manufacturing a combination product for oral inhalation. A factorial design was used to study the effects of process and formulation parameters. A 6–7-fold difference in *in vitro* respirable fractions were seen for the powders obtained by using a different combination of the process parameters. The co-spray dried system, which displayed best *in vitro* deposition characteristics, showed a 2.6-fold increase in the *in vitro* twin impinger respirable fraction and better dose uniformity compared with the physical mix of micronised powders.

2.4. PulmoSol™ powder technology

PulmoSol™ is a powder technology that allows the preparation of spray dried insulin compositions by stabilising the peptide/protein in an amorphous glass matrix. Under controlled conditions, insulin is preserved chemically and physically, in the form of a powder that presents good dispersibility and small particle size, suitable for pulmonary delivery. This technology was developed by Nektar Therapeutics (previously Inhaled Therapeutics), as part of their research towards the development of the first insulin dry powder inhaler - Exubera® [33–35].

An aqueous solution with a total constituent concentration between 1 and 5% (w/w), containing recombinant human insulin, mannitol (bulking agent/stabilising agent), glycine (bulking agent) and sodium citrate (buffering agent) is prepared. The solution is spray dried using a two-fluid nozzle with a set rate of flowing solution and atomisation gas resulting in an air liquid ratio of 5 and, an inlet temperature between 140 and 150 °C, resulting in an outlet temperature ranging from 60 °C to 80 °C [36,37]. As droplets are atomised and contact with the drying gas, evaporation takes place from the saturated vapour film which is quickly established at the droplet surface. When, at the initial drying rate, the dissolved solute is not transported to the droplet centre by means of diffusion and convection, a viscous layer (or crust) of material is created at the surface. As drying continues the crust is unable to flow as rapidly as the shrinking of the particle as the solvent evaporates, resulting in three different morphologies depending on the properties of the crust: solid hollow spheres, dimpled (crust buckles) or wrinkled particles (crust folds) [27,35]. The non-displacement of solute into the droplet centre is characteristic of systems where the calculated Peclet number (the ratio of time for solute diffusion from the droplet surface to its centre to time for droplet drying) is above 1 [27,38]. Studies by Vehring [35] predict the displacement and concentration of insulin to/at the droplet surface, due it being the component of highest molecular weight and highest percentage in the formulation; insulin then is the agent responsible for particle wrinkling. Hence, PulmoSol™ powders present rugged (wrinkled) or raisin-like particles (Fig. 1).

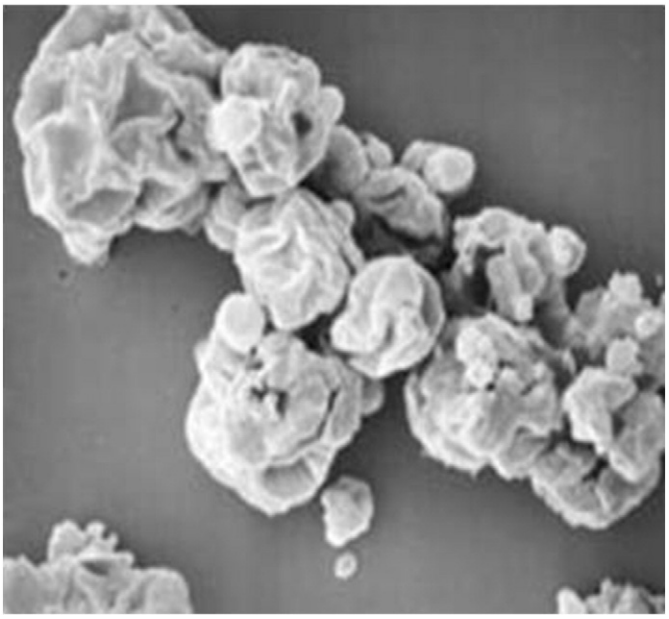

Fig. 1. Scanning electron micrograph of PulmoSol™ particles (from [145] with permission).

The physicochemical characteristics of PulmoSol™ powders (Exubera®) are: a true density of approximately 1.48 g/cm^3, bulk density of 0.2 g/cm^3; mass median diameter and mass median aerodynamic diameter between 1 and 5 μm; surface area range from 4 to 13 m^2/g; a moisture content of 2% (w/w); a single glass transition of approximately 115 °C when completely dry, and of 78–95 °C when the moisture content is within storage specifications; and excellent physical and chemical stability allowing 2 years of shelf life at room temperature [35,37]. These particles are highly soluble and quickly dissolve upon reaching the alveoli, where they pass a single cellular layer into the circulation, resulting in an insulin pulmonary bioavailabily of 8 to 25% [33,39].

2.5. Technosphere® powder technology

The Technosphere® platform was developed by MannKind Corporation (US) for the delivery of insulin to the systemic circulation *via* the lungs for diabetes mellitus treatment, as in the Afrezza® product which is in the late stages of commercial development. This technology is based on the capacity of an excipient, fumaryl diketopiperazine (FDKP) (MannKind's proprietary inert excipient) a substituted diketopiperazine, to self-associate forming microparticles in a range between 0.5 and 10 μm, more specifically 2–3 μm (geometric particle size and MMAD) for insulin particles [40–43]. FDKP constitutes the particle matrix and primary component of the Technosphere®. The diketopeperazines are rigid planar hexagonal rings with opposing heteron atoms and unbonded electron pair that can constitute the building blocks of a pH-dependent, self-assembling (*via* intramolecular hydrogen-bonding) system; microparticles are formed in the presence of the drug to be encapsulated by: (a) acidification of weakly alkaline solutions of a diketopiperazine derivative that contains one or more acidic groups, (b) basification of acidic solutions of a diketopiperazine derivative that contains one or more basic groups, or (c) neutralisation of an acidic or basic solution of a zwitterionic diketopiperazine derivative that contains both acidic and basic groups [40–42,44,45]. Spray drying, phase separation and solvent evaporation are the preferred methods for microparticles production [41,46]. Therefore, particles can be either crystalline or amorphous (Fig. 2); with crystalline particles prepared by the latter two methods, and amorphous particles prepared *via* spray drying solutions or suspensions of the salt form of FDKP with the drug/API [46]. The microparticle size is controlled by choosing the appropriate process settings in spray drying

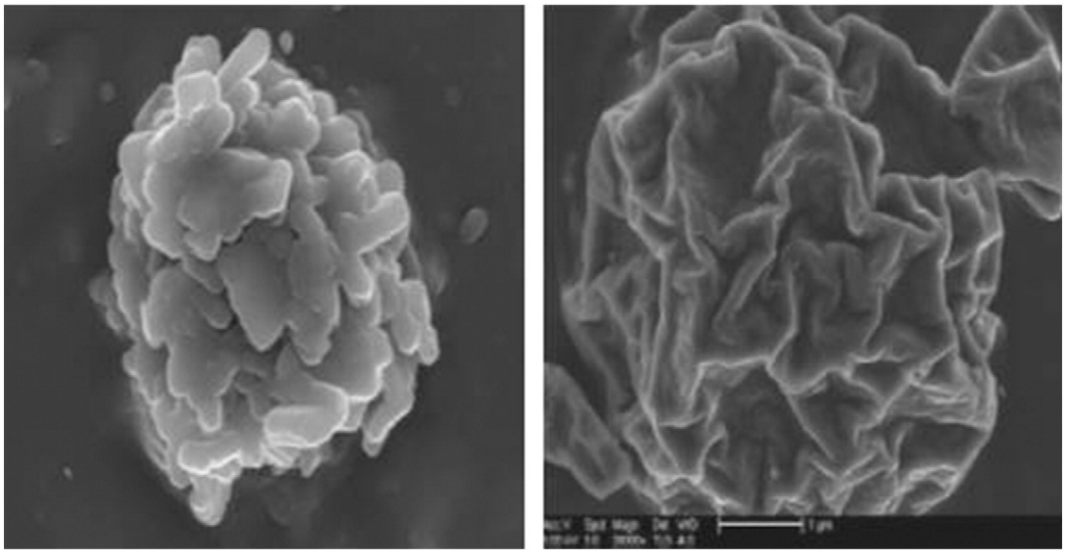

Fig. 2. Scanning electron micrograph of Technosphere® (left) crystalline particle and (right) amorphous particle (from [46] with permission).

and crystallisation, requiring no further processing for particle size reduction [41,46]. Leone-Bay et al. [46] have simplified the explanation of the microparticles self-assembly/morphology by comparing it to a deck of cards: each card represents an FDKP nanocrystal and the sphere constructed from the cards represents a Technosphere particle, with the back and front faces of the cards providing a large surface area, and the spaces between the cards a high internal porosity, resulting in low density and high dispersibility for deposition in the distal airways. In the precipitation process, it traps and microencapsulates the API present in the solution [42,43,46].

Upon inhalation, the Technosphere® dissolves immediately at the lung's physiological pH (6.5) due to FDKP's high solubility at pH ≥ 6, with rapid (approximately 15 min) and efficient absorption of the API to the systemic circulation. Once in the plasma, within seconds, the FDKP molecules de-associate and release the API. The excipient is not metabolised and is excreted as the ammonium salt in the urine within hours of administration [42,43,46,47]. Insulin Technosphere® has a pulmonary bioavailability of 26% [48].

Finally the Technosphere® platform can be used to deliver assorted APIs from peptides and proteins to inorganic and organic compounds, such as: insulin, heparin, calcitonin, felbamate, parathyroid hormone, growth hormone, erythropoietin, zidovudine, didanosine, G-CSF, lamotrigine, chorionic gonadotropin factor, luteinising releasing hormone, β-galactosidase and argatroban; in a wide range of loadings between 0.01% and 90% [40,41,44].

2.6. Liposome-based particulate systems

In liposomal dry powder formulations, drug encapsulated liposomes are converted into a dry powder form by freeze drying [49,50], spray drying [51], or spray freeze drying [52]. Such systems are formulated with phospholipids similar to endogenous lung surfactant and have potential for controlled release and enhanced stability of the bio/active material [53]. The physical stability of liposomal formulations has been shown to be improved in the dry state [51,53] and dry powder systems avoid the stability issues that may be seen with solutions during nebulisation. Liposomes in the solid state have been called liposomes, lipospheres, and proliposomes [53].

Willis et al. [53] have recently presented a review of the various therapeutic agents that have been formulated and successfully delivered by liposomal dry powder formulations. Such therapeutics include corticosteroids, β_2-selective receptor agonist, mast cell stabiliser, antimicrobials, immunosuppressants, antituburcular and chemotherapetics agents. Drug encapsulation in liposomes has been shown to improve the therapeutic effect and index of pharmaceutical drugs.

A recent study assessed the use of simple air jet nebulisation to produce submicron liposome aerosol powders through control of precursor suspension colloidal properties [54]. Colloidal properties of the suspension and particle type, vis-a-vis payload size and controlled release, were varied by changing liposome type (unilamellar and oligolamellar) and lipid concentration. The authors found that suspensions of oligolamellar liposomes were more suitable than unilamellar liposomes for the generation of submicron particles with controlled release properties, because of their larger internal volume (drug-loading capacity) and lower disruption (change in dye-release rates) during aerosol generation.

2.7. Porous particle technologies

2.7.1. Large porous particles (LPPs)/AIR®/ARCUS™

AIR® is a phospholipid-based porous microparticles platform technology developed by Advanced Inhalation Research in 1997 and later acquired by Alkermes (in 1999). The particles produced have been referred to as large porous particles (LPPs). Recently, Civitas Threapeutics (US), a spin-out pulmonary delivery business of Alkermes, relaunched the LPPs as ARCUS™ technology.

Edwards et al. [55] proposed that particles with a geometric diameter (d) greater than 5 μm and with a low density (less than 0.4 g per cubic centimetre) could present an aerodynamic diameter smaller than 5 μm and thus be suitable for pulmonary drug delivery. In the original Science paper in 1997, Edwards et al. [55] suggested that LPPs aerosolized better from DPIs than non-porous particles due to the former's low density, larger size and their consequent lower tendency for aggregation. Additionally it was suggested that larger particles could avoid phagocytic clearance in the lungs more effectively than smaller non-porous particles.

2.7.1.1. Double emulsion solvent evaporation production method for LPPs. The original production process of large porous particles (LPPs) was based on the double emulsion solvent evaporation technique [55]. The aqueous internal phase consists of an aqueous solution of active pharmaceutical ingredient, which may contain other ingredients such as polymeric additives (*e.g.* poly(lactic-co-glycolic) acid (PLGA)), cyclodextrin, solubilising agents or pH modifiers (*e.g.* acetic acid). The organic external phase may be composed of a polymeric carrier such as PLGA or PEG (polyethylene glycol) dissolved in dichloromethane or methylene

chloride with the addition of an emulsifier (*e.g.* phosphatidylcholine). The aqueous internal phase and organic external phase are emulsified together by homogenisation to form a primary emulsion and combined, by injecting or pouring, with a secondary aqueous phase containing various concentrations of polyvinyl acetate as well as necessary additives such as sodium chloride [56]. The double emulsion is further subjected to stirring, during which the organic solvent evaporates resulting in LPP formation and hardening. Subsequently LPPs are isolated by centrifugation, washing and freeze drying (Fig. 3). Edwards et al. [55] compared testosterone non-porous particles ($d < 5$ μm) prepared by a single emulsion technique with testosterone LPPs (based on poly(lactic acid-co-glycolic acid) or poly(lactic acid-co-lysine-graft-lysine) matrix) ($d > 5$ μm) (Fig. 4). The measured respirable fraction of LPPs was found to be three times larger than non-porous particles (50–60% vs 20%). *In vivo* studies in rats proved the efficiency of delivery of LPPs, as lower levels of tracheal deposition were found (46%) in comparison with the non-porous particles (79%).

In the same paper by Edwards et al. [55] the efficacy of PLGA based LPPs ($d > 5$ μm) and non-porous particles for the intratracheal delivery of insulin to rats was compared. Only the LPPs resulted in elevated blood levels of insulin beyond 4 h, with relatively constant insulin release for 96 h For the LPPs, insulin bioavailability relative to subcutaneous injection was 87.5%, compared to 12% for non-porous particles. The authors suggested that the appearance of exogenous insulin in the bloodstream several days after inhalation indicated that LPPs achieve long, nonphagytosed lifetimes in the deeps lungs. Lung lavage (in rats) was performed immediately after inhalation and 48 h after inhalation. For non-porous particles 30 ± 3% of phagocytic cells contained particles

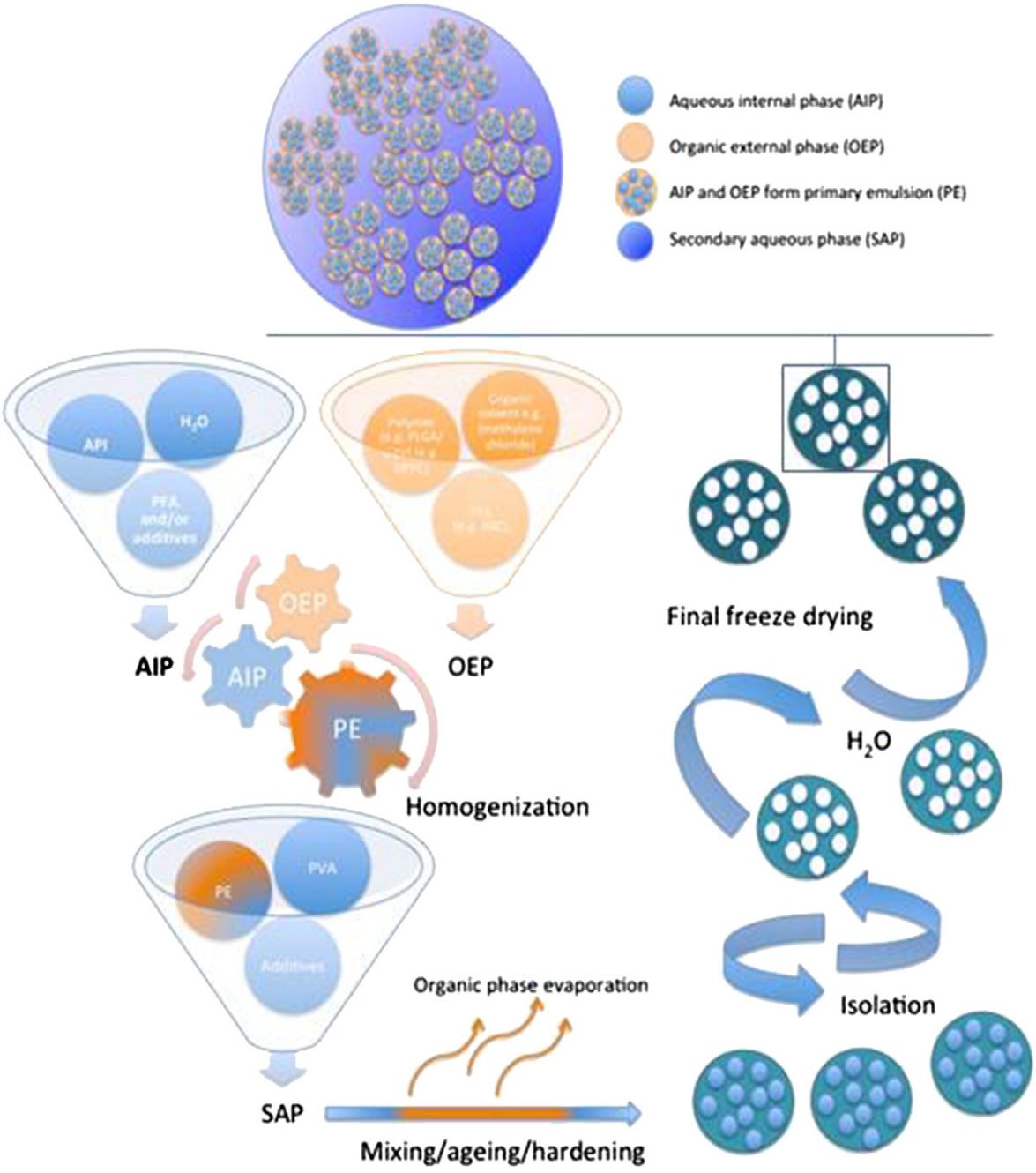

Fig. 3. Double emulsion scheme illustrating: aqueous internal phase (AIP), organic external phase (OEP), AIP and OEP form primary emulsion (PE) and secondary aqueous phase (SAP), and production flow of LPPs using the double emulsion solvent evaporation (DESE) approach.

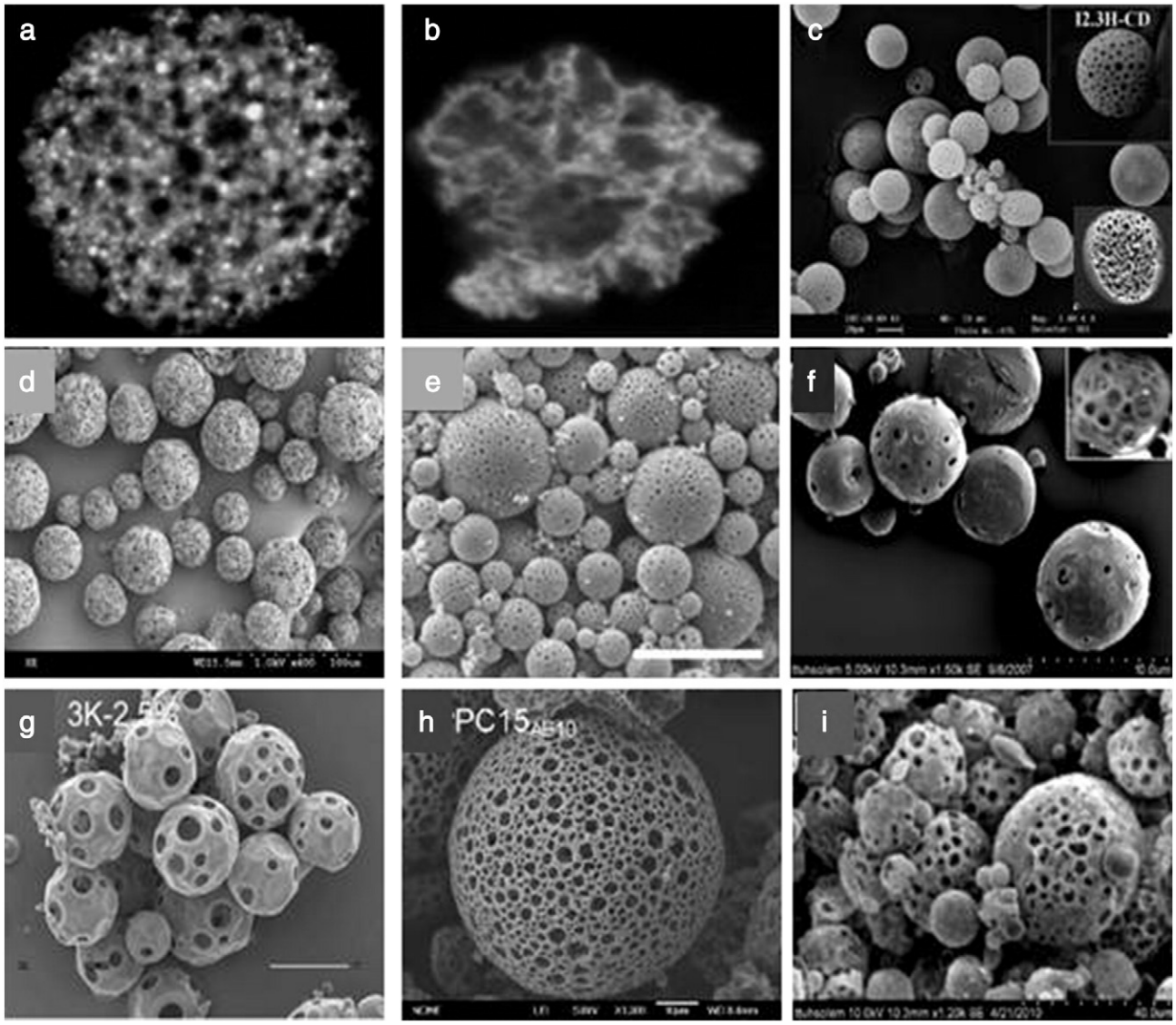

Fig. 4. Scanning electron micrographs of (a) poly(lactic-co-glycolic) acid (PLGA) large porous particles (LPP) (from [55] with permission), (b) poly(lactic acid-co-lysine-graft-lysine) (PLAL-Lys) LPP (from [55] with permission), (c) bovine insulin (INS(b)) LPP (from [57,58] with permission), (d) bovine serum albumin (BSA) LPP (from [59] with permission), (e) camptothecin (CT) LPP (from [61] with permission), (f) low molecular weight heparin (LMWH)-PLGA-polyethyleneimine (PEI) LPP (from [60] with permission), (g) double emulsion solvent evaporation (DESE)–ammonium bicarbonate (ABC)–PLGA-Placebo-LPP (from [62] with permission), (h) DESE-ABC-PLGA–dipalmitoylphosphatidylcholine (DPPC)-1,2-dioleoyl-3-trimethylammonium-propane (DOTAP) LPP (from [63] with permission), (i) prostaglandin E1 (PGE1)-PLGA-PEI (polyethylene imine) LPP (from [65] with permission).

immediately after inhalation and 39 ± 5% did so after 48 h. These figures contrasted with 8 ± 2% and 12.5 ± 3.55% for LPPs, immediately after inhalation and after 48 h, supporting the theory for reduced phagocytic clearance for LPPs.

Further studies on LPPs produced by the double emulsion solvent evaporation method by Ungaro et al. [57,58], Kwon et al. [59], Rawat et al. [60] and Meenach et al. [61] explored the use of different excipients and APIs for LPP production: PLGA [55,56], hydroxypropyl-beta-cyclodetrin (HPβCD) [57,58], sulfobutyl ether β-cyclodextrin sodium salt [59], sucrose acetate isobutyrate [59], acetylated dextran [61], Span 60 [61], stearylamine [61], polyethylene imine [61], bovine insulin [57,58], bovine serum albumin [59], campthotecin [61] and low molecular weight heparin [60] (Fig. 4). Particles presented a MMAD ranging from 3 to 17 μm, high fine particle fractions and emitted doses, and extended release profiles [57–61].

Rawat et al. [60] also observed that incorporation of polyethylene imine (PEI) in the aqueous internal phase altered the morphology of LPPs, visibly increasing the porosity (Fig. 4). They concluded that PEI worked as a pore forming agent in formulations processed by the conventional double emulsion solvent evaporation production process. Pore formation was attributed to electrostatic complex formation between negatively charged low molecular weight heparin and PEI. As a result, the space occupied by the dispersed drug may have increased along with the amount of bound water. Alternatively, differences between the osmotic pressure of the internal and external aqueous phases may have played a role in the increase in porosity. As PEI is an osmotically active polycation, its presence in the aqueous internal phase may lead to an increased influx of water, resulting in larger aqueous droplets during emulsification. Removal of water during lyophilisation leaves void space in the particles, making them more porous and with relatively larger-diameter pores than in formulations without PEI [60].

Yang et al. [62] explored further the use of pore forming agents. Ammonium bicarbonate was added to the aqueous internal phase or primary emulsion prior to mixing with the secondary aqueous phase, resulting in highly porous PLGA LPPs loaded with doxorubicin hydrochloride (Fig. 4). Particles presented MMADs between 4.6 and 5.7 μm and FPFs between 16 and 34%, as well as reduced macrophage uptake and prolonged drug release.

The approach reported by Yang et al. [62] was also used by Ungaro et al. [63] where ammonium bicarbonate was dissolved in the AIP. The LPPs produced were composed of PLGA, 1,2-dioleoyl-3-trimethylammonium-propane and dipalmitoylphosphatidylcholine (DPPC) and were loaded with rhodamine B isothiocyanate–dextran as a model hydrophilic macromolecule. These LPPs were considered to be gas-foamed LPPs (Fig. 4) since, during the production process, ammonium bicarbonate degraded releasing ammonia and carbon dioxide gases and resulting in pore formation in the prepared particles. The LPPs presented favourable *in vitro* and *in vivo* (rodents) deposition.

Gupta et al. [64] reported an interesting modification to the conventional aproach to double emulsion solvent evaporation PLGA LPP production by incorporating/dissolving prostaglandin E1 (PGE_1), which is hydrophobic, in the organic external phase. Particle MMADs varied from approximately 1 μm to 4 μm, and showed good metabolic stability and prolonged release of PGE_1 after pulmonary administration. Later, in 2011, Gupta and Ahsan [65] reported a modified aproach to PLGA-PGE_1 LPP production where the API was incorporated into the aqueous internal phase by solubilisation in a minimum quantity of ethanol. The aqueous internal phase was also supplemented with polyethylene imine as a pore forming agent and drug-loading capacity enchancer (Fig. 4). All reported MMAD values were below 5 μm.

2.7.1.2. Production of LPPs by spray drying. An alternative aproach to the production of LPPs was introduced by Ben-Jebria et al. in 1999 [66]. This group implemented spray drying instead of isolation and final freeze drying (Fig. 3) in order to separate solids from aqueous and organic phases. Ben-Jebria et al. [66] produced composite salbutamol sulphate LPPs composed of human serum albumin, lactose and DPPC by spray drying from 85% ethanol in water solution. The LPPs (Fig. 5) produced presented MMAD values below 4.7 μm and FPF of approximately 50% compared to 16% measured for non-porous particles. In rodent *in vivo* experiments LPPs proved to have an extended release profile of salbutamol sulphate, resulting in an absence of cardio-respiratory side effects as well as a lack of acute inflammatory responses following pulmonary adminstration.

Also in 1999, Vanbever et al. [67] published a study where salbutamol sulphate, human insulin or 17-β-estradiol was (individually) dissolved in an appropriate solvent (water in the case of salbutamol sulphate and insulin, and 95% ethanol in the case of 17-β-estradiol). Water soluble additives (lactose, human serum albumin, sodium hydroxide or hydrochloric acid) were dissolved together with the API in the aqueous solution, while water insoluble constituents (DPPC) were dissolved in the ethanol solution. Both solutions were mixed prior to spray drying. MMAD values of the spray dried LPPs (Fig. 5) varied, depending on drug and drug loading, from 4.8 to 7.5 μm (by Andersen cascade impactor) or 2.6–5.3 μm (by Aerosizer™ analysis).

Dunbar et al. [68], continuing the LPP spray drying studies, evaluated the *in vitro* and *in vivo* dose delivery characteristics of two LPP-placebo formulations with different MMADs corresponding respectively to approximately 2.9 μm and 5.0 μm. Results of the *in vitro* experiment correlated well with *in vivo* findings where, at comparable emitted doses of ~90%, particles with a smaller MMAD value had lung deposition of ~60%, while larger MMAD particles deposited only in range of 40–45%.

A recent study published by Pham et al. [69] is the first example of the inclusion of a functional excipient in LPPs with a view to physicochemical modification of the API, where hyaluronic acid in combination with DPPC were found to inhibit polymorphic transformation and partially inhibit crystal growth/nucleation of pyrazinamide and enabled stable, partially crystalline spherical particles adapted for deep lung delivery to be obtained. LPPs were obtained by spray drying of ethanolic solution of DPPC combined with an aqueous solution of pyrazinamide and D,L-leucine and hyaluronic acid with the addition of ammonium bicarbonate (Fig. 5).

2.7.1.3. Modified production processes for LPPs. Steckel and Brandes [70] expanded the conventional approach to solution or suspension spray drying for the production of LPPs. LPPs of salbutamol sulphate were

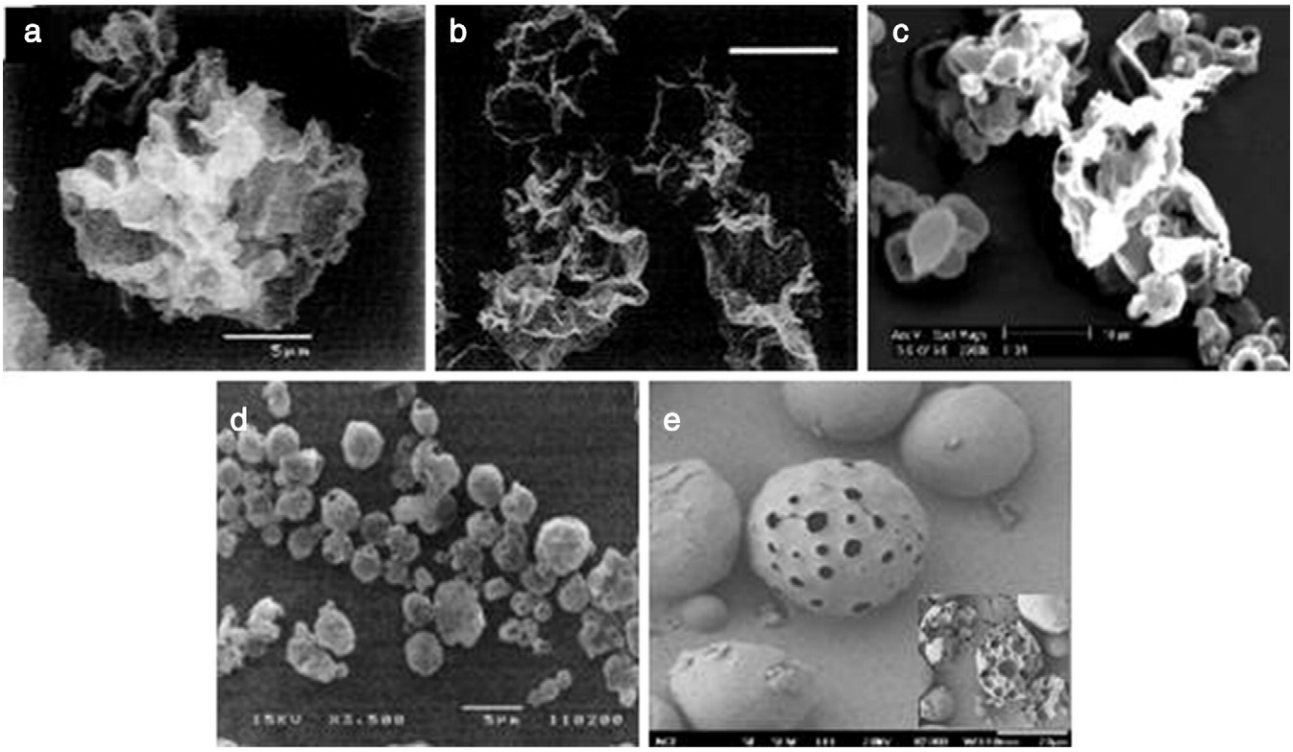

Fig. 5. Scanning electron micrographs of large porous particles (LPPs) obtained by spray drying: (a) salbutamol sulphate LPP (from [66] with permission), (b) dipalmitoylphosphatidylcholine (DPPC)-LPP (from [67] with permission); or by emulsion solvent evaporation-$scCO_2$ processing: (c) salbutamol sulphate LPP (from [70] with permission), (d) deslorelin-PLGA-LPP (from [71] with permission), (e) celecoxib-PLGA-LPP (from [73] with permission).

produced by spray drying of a "compressed emulsion" (Fig. 5). The emulsion, in contrast to the double emulsion solvent evaporation technique, was composed of an organic ("oil") internal phase, which was a propellant (Solkane™ 227). The aqueous external phase was composed of water soluble salbutamol sulphate, phosphatidylcholine, poloxamer 188 and calcium chloride dihydrate, with or without addition of dichloromethane and HPβCD. Depending on process conditions and formulation composition, FPF values varied from 20% to up to 59%.

Koushik et al. [71,72] introduced an alternative production method for LPPs where conventional deslorelin-PLGA-(HPβCD) microparticles were prepared using an emulsion solvent evaporation method and reprocessed using a supercritical compressed solution of carbon dioxide ($scCO_2$) (Fig. 5). PLGA dissolved in methylene chloride was combined with a methanolic solution of deslorelin with or without of HPβCD phosphate buffer solution to produce the organic ("oil") internal phase. The organic ("oil") internal phase was dispersed in an aqueous solution of polyvinyl acetate. Formed microparticles were isolated by centrifugation, washed and freeze-dried. The prepared microparticles were subsequently held under pressure in $scCO_2$. Supercritical fluid processing was able to modify non-porous microparticles and produce LPPs using a relatively low process temperature of 33 °C.

A similar aproach to produce celecoxib LPPs was reported recently by Dhanda et al. [73] who produced PLGA microparticles by the emulsion solvent evaporation technique through homogenisation of the primary emulsion. The oil phase was composed of: celecoxib, PLGA and dichloromethane and the disperse phase was a polyvinyl acetate aqueous solution. The primary emulsion was subsequently diluted with the aqueous solution and stirred to evaporate the dichloromethane. Microparticles were isolated, washed, freeze-dried and reprocessed using $scCO_2$ to produce LPPs (Fig. 5). Celecoxib–PLGA LPPs proved to be better in sustaining drug levels in the lungs and improved the lung accumulation index following a single administration, compared to conventional non-porous particles or plain drug.

2.7.2. PulmoSpheres®

As seen previously, the spray drying process emerged as a useful approach to the production of large porous particles. Spray drying also became the main production process approach for the PulmoSphere® technology [74]. In contrast to solution spray drying, which is used to produce LPPs, Weers et al. [74] filed a patent covering spray drying of porous microparticles from an emulsion-based feed (Fig. 6). PulmoSpheres® differ from LPPs in that the geometric particle size is less than 5 μm. The porous nature of the particles allows for reduced particle–particle interactions and reduced cohesion. The porous nature thus allows for improved flowability and aerosolisation of particles.

Dellamary et al. [75] described the production process of PulmoSpheres® containing cromolin sodium, salbutamol sulphate or formoterol fumarate. The process may be divided into a number of different unit processes of which the first two are: preparation of the emulsion and, the aqueous solution containing dissolved API and additive (*e.g.* poloxamer). In contrast to the double emulsion solvent evaporation technique, the emulsion used in PulmoSphere® technology is of the oil-in-water (o/w) type, where the dispersed phase is composed of fluorocarbon (*e.g.* perfluorodecalin or perfluoro-octyl bromide (Perflubron™), while the aqueous continuous phase contains emulsifier (*e.g.* phosphatidylcholine or distearoylphosphatidylcholine (DSPC). The homogenised o/w emulsion is mixed with aqueous solutions carrying the API and other constituents and spray dried. During spray drying solids phase-separate from the evaporating solvent, the water

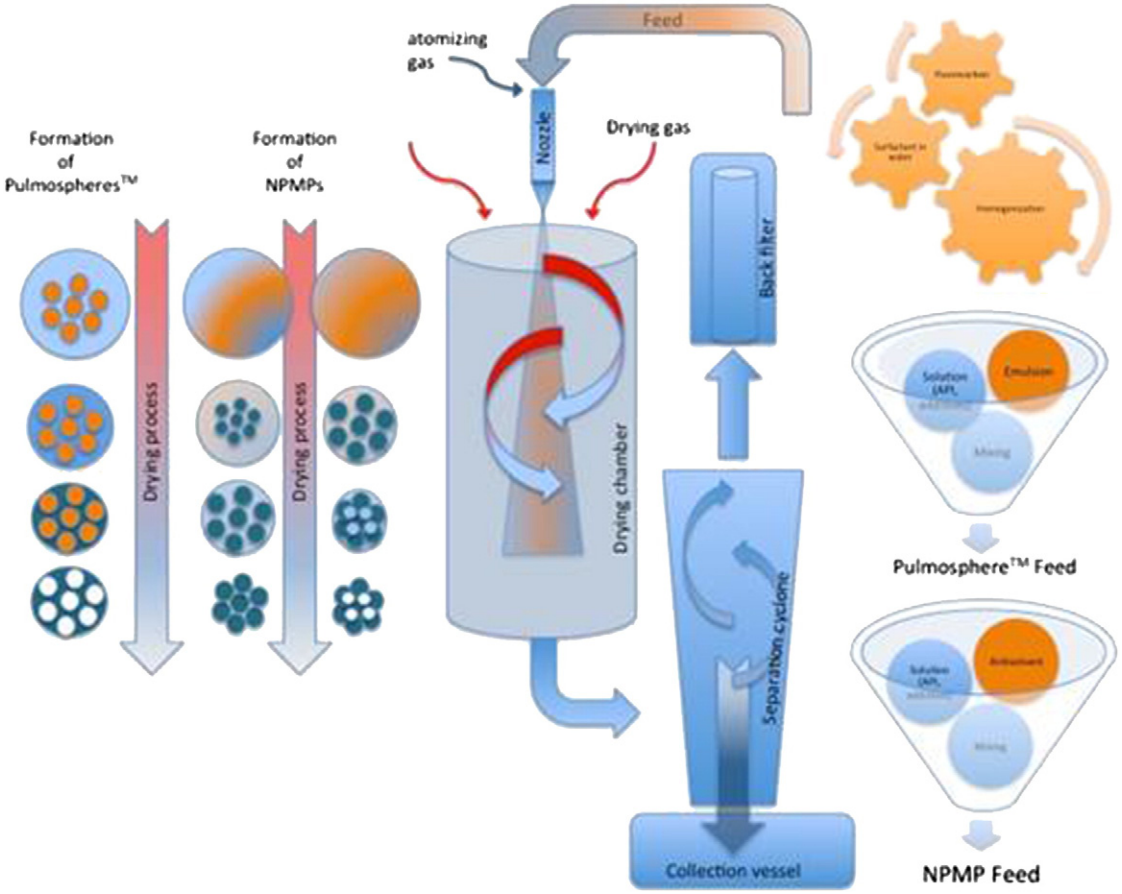

Fig. 6. Scheme comparing production processess and particle formation of PulmoSpheres™ and NPMPs.

evaporates first, followed by the fluorocarbon which, on evaporation from the particle surface, acts as a pore-former (Fig. 7).

Bot et al. [76], Smith et al. [77], Hirst et al. [78] and Tarara et al. [79] reported on PulmoSpheres® produced using different APIs: hIgG [76], gentamicin sulphate [77], salbutamol sulphate [78] and budesonide [79] (Fig. 7). In all cases, as well as in studies by Weers et al. [74] and Dellamary et al. [75], particles produced were redispersed in fluoroalkane and packaged as pMDIs.

In 2002 Duddu et al. [80] introduced the idea of the application of a modified PulmoSphere® technology for dry powder inhalers. In contrast to previously described studies, API (budesonide) was processed in microcrystalline form instead of being dissolved in an aqueous solution. Microcrystals were combined and homogenised with a pre-prepared emulsion of perflubron with DSPC in water. Secondly the suspension-emulsion was combined with an aqueous solution of calcium chloride dihydrate with lactose monohydrate and spray dried. The produced PulmoSpheres® (Fig. 7) were compared to a budesonide Pulmicort® Turbohaler® preparation (containing only pelletized microspheres of API) in a single centre, three-way crossover study conducted in 10 healthy subjects. Pulmonary deposition of budesonide PulmoSpheres® was around 60%. Mean peak plasma budesonide levels for the PulmoSphere® formulation were approximately two times greater than for the Pulmicort® preparation. Median t_{max} was observed at 5 min for the PulmoSphere® preparation compared to 20 min for Pulmicort®, with comparable mean AUCs.

In 2003 Newhouse et al. [81] published a study comparing tobramycin PulmoSpheres® inhaled through a Turbospin DPI (see Section 4) to commercial nebulized tobramycin product (TOBI®) in a five-period, open-label, nonrandomized crossover study including fourteen healthy volunteers. Mean whole-lung deposition of the PulmoSphere preparation was around 34% compared to approximately 5% for TOBI®. Peak tobramycin concentrations in serum for PulmoSpheres® was about three times larger than for TOBI®, while serum area under the curve was about two times greater. Median times to C_{max} were comparable for both preparations.

Geller et al. [82] reported on a multi-centre, open-label, sequential-cohort, single-dose, dose-escalation study. The efficacy of encapsulated PulmoSphere®-tobramycin preparation (Fig. 7) inhaled through a T326 DPI (Podhaler™) (see Section 4) was compared to 300 mg dose of tobramycin solution for inhalation (TSI [TOBI®]). Serum tobramycin pharmacokinetic profiles were similar for both preparations. Four capsules of 28 mg PulmoSphere®-tobramycin produced comparable systemic exposure to 300 mg TSI, in less than one-third the administration time.

In March 2013 the FDA approved TOBI® Podhaler™ to treat a type of bacterial lung infection in cystic fibrosis patients.

A recent study by Weers et al. [83] was focussed on dose emission characteristics of placebo PulmoSphere® particles administered as dry powders with a portable, blister-based dry powder Simoon Inhaler. The study included 69 asthma/COPD subjects. *In vitro* measures of particle deposition were found to be largely independent of the inhalation manoeuver (flow rate, inhaled volume, ramp time) across the broad range of inhalation profiles observed in the study.

2.7.3. Emulgent-free nanoporous/nanoparticulate microparticles (NPMPs)

Excipient-free nanoporous/nanoparticulate microparticles (NPMPs) were introduced in 2008 by Healy at al. [84], who reported on the

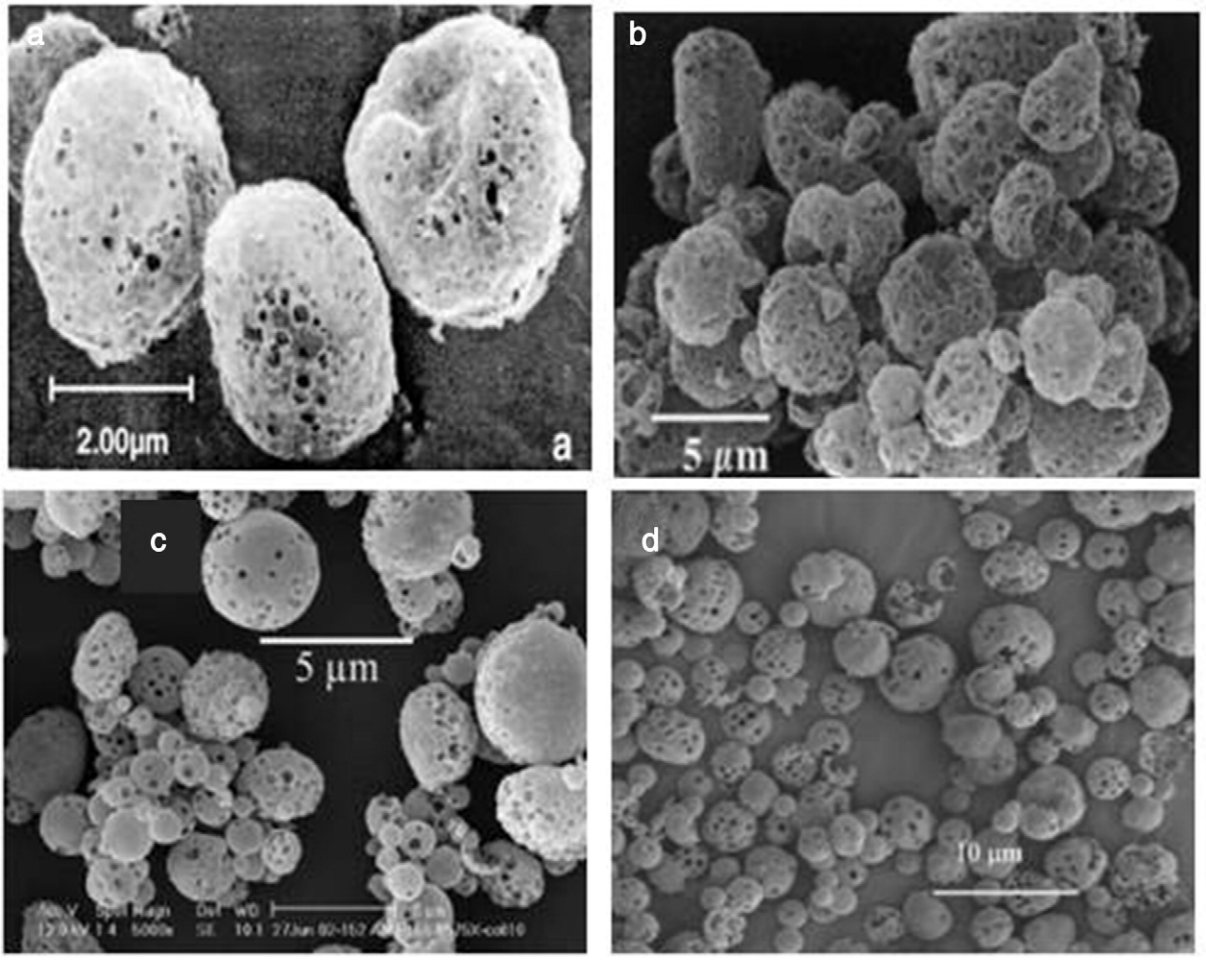

Fig. 7. Scanning electron micrographs of PulmoSpheres™: (a) sodium cromoglicate (from [75] with permission), (b) budesonide (from [80] with permission), (c) budesonide (from [79] with permission), (d) tobramycin (from [82] with permission).

production of (in contrast to LPPs and PulmoSpheres) excipient-free porous microparticles by spray drying from a mixed solvent/antisolvent system. The production of NPMPs of different materials such as bendroflumethiazide [84], budesonide [85], sodium cromoglicate [86], trehalose [87,88], raffinose [87,88], sugar loaded with lysozyme [87] or trypsin [89], p-amino salicylic acid [90] and budesonide ambroxol hydrochloride [91] has been reported (Fig. 8). Ammonium carbonate was used as a pore forming agent in solutions with bendroflumethiazide and budesonide [84,85]. Different co-solvent systems can be used in the NPMP production process, with ethanol/water and methanol/water being reported as suitable solvents for hydrophobic API/excipients [84,85,90,91] and water/methanol/butyl acetate and methanol/butyl acetate [86–89] being suitable for more hydrophilic materials.

The mechanism of NPMPs formation is proposed as follows [92]: during the atomisation stage of the spray drying process, droplets are formed containing the solute (excipient or drug or both) in the co-solvent mix; rapid drying of these droplets proceeds on contact with the warm drying gas and the more volatile solvent phase in which the solute is more soluble, evaporates to a greater extent, resulting in the droplet becoming richer in the less volatile solvent component, in which the solute is less soluble. The fall in the solubility of the solute may be dramatic and it may condense out initially as a nanosized liquid phase within the droplet. As drying proceeds and further solvent loss occurs, the solute phase droplets become less fluid and come closer together, and the solute may precipitate out as primary nanoparticles which agglomerate together either at the particle surface (forming an outer shell) or within the particle, leading to nanoparticulate microparticle formation [85,87,92].

All NPMPs produced present, in general, a small median geometric particle size (<3 μm); lower bulk and tap densities than equivalent spray dried non-porous particles, due to the porous nature. Reported NPMPs were all amorphous in nature with the exception of NPMPs of PAS [90] which were crystalline. NPMPs demonstrated improved *in vitro* deposition (FPF 50–80% and ED up to 80%) when compared to non-porous particles and commercial products such as Pulmicort® Turbohaler®, Cyclohaler® budesonide Cyclocaps® and Intal™ [85,86]. The improved aerosolisation properties of NPMPs may be attributed to reduced interparticulate contact as a result of the porous structure, resulting in reduced powder cohesiveness [85–87,89]. A trend of increasing FPF with increasing specific surface area, attributable to the porosity of the particles has been reported [88].

2.8. Trojan particles

2.8.1. Trojan microparticles-LPNPs

Tsapis et al. [38] combined the drug release and delivery potential of nanoparticle (NP) systems with the ease of flow, processing, and

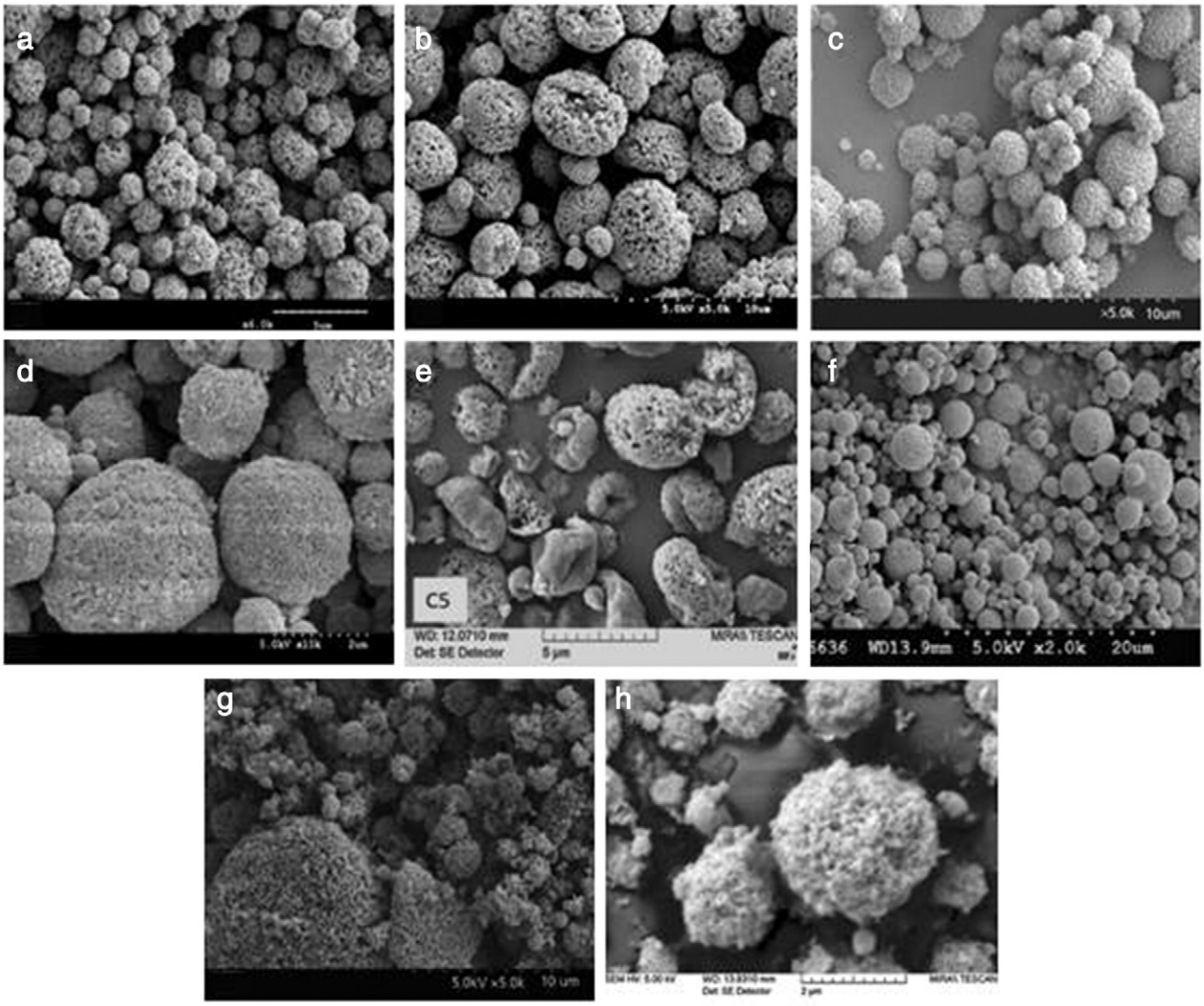

Fig. 8. Scanning electron micrographs of selected NPMPs materials: (a) bendroflumethiazide (from [84] with permission), (b) budesonide (from [85] with permission), (c) p-aminosalicylic acid (PAS) (from [90] with permission), (d) sodium cromoglicate (from [89] with permission) (e) budesonide ambroxol HCl (from [91] with permission), (f) raffinose (from [87] with permission), (g) trypsin (from [89] with permission) (h) trehalose (from [88] with permission).

aerosolisation potential of large porous particle (LPP) systems by spray drying solutions of polymeric and nonpolymeric NPs into thin-walled macroscale structures. They referred to the spray dried particles as large porous nanoparticulate (LPNP) aggregates or Trojan particles (Fig. 9). These Trojan microparticles (d > 5 μm) exhibit much better flow and aerosolisation properties than the constituent NPs. Under physiological conditions they should dissolve to produce NPs. The NPs are held together in the Trojan particles by physical means, such as Van der Waals forces, or within a matrix of added ingredients such as biopolymers or phospholipids [38].

Tsapis spray dried three different systems to produce Trojan microparticles: (1) polystyrene nanoparticles were added to a solution comprised of ethanol/water (7:3 vol/vol) containing dipalmitoylphosphatidylcholine, 1,2-dimyristoyl-sn-glycero-3-phosphoethanolamine and lactose with or without hydroxypropylcellulose; (2) silica nanoparticles were added to a solution of similar composition to (1) above, except that water was replaced by 25 mM Tris buffer pH 9.25 to ensure colloidal silica stability and (3) polystyrene nanoparticles were added to a solution of bovine serum albumin in phosphate buffer with the addition of ammonium bicarbonate. Nanoparticulates used to prepare the tojan particles ranged in diameter from 25 nm to several hundred nm [38].

Other groups have since used the Trojan microparticle concept to deliver nanoparticles to the lungs [93–95].

2.8.2. Trojan microparticles/magnetically targeted dry powder aerosols

A number of groups have investigated magnetisation as a means of targeting drugs to specific regions of the lung and proposed this in the treatment of lung cancer for example, a condition which is often only associated with one side or one lobe of the lung and where there is a concern that conventional aerosol treatment may damage healthy parts of the lungs [96].

The concept of magnetisation involves incorporating magnetically active particles to a chemotherapeutic drug, such that the particles, as well as the attached drug, can be guided to a specific location in the body using a strong external magnet [97,98].

As far back as 1996, Lübbe et al. performed the first clinical trials for the treatment of breast cancer by magnetic carriers of epirubicin [99]. These trials followed pre-clinical studies [100] that documented tolerance and efficacy. In the first trials, epirubicin was ionically bound to a modified carbohydrate layer on iron-oxide nanoparticles. The authors observed the accumulation of nanoparticles in the target area after exposure to the magnetic field.

When superparamagnetic iron-oxide nanoparticles (SPIONs) are exposed to an alternating magnetic field the oscillation of the magnetic moment within the particles, and loss of magnetic hysteresis, results in a release of energy as heat to the surrounding tissues, thus contributing to tumour cell death through hyperthermia [100].

Upadhyay et al. [101] used oil-in-water emulsification to prepare particles with SPIONs and drug (budesonide) embedded within a lipid matrix. The lipid system presented thermo-sensitive characteristics demonstrating accelerated rate of drug release at hyperthermic temperatures (45 °C). Upadhyay et al. [101] suggested that a temperature of 45 °C was feasible to achieve through external stimulation, facilitated by alternating the magnetic field.

The model drug and SPION loaded lipid system was magnetically active and movable using simple permanent magnets. The produced inhalation dry powder presented promising inhalation performance, with an inhalable fine particle fraction of 30%, as measured for the formulation loaded into HPMC capsules and delivered using an Aerosolizer inhaler.

Tewes et al. [94] prepared SPIONs-loaded Trojan microparticles by spray drying SPIONs, PEG and HPβCD, ammonium carbonate and magnesium stearate. The resulting particles were spherical with a porous surface and a MMAD of 2.2 ± 0.8 μm (with the powder loaded into a gelatin capsule and delivered by a Handihaler® into a Next Generation Impactor). In the presence of a magnetic field on stage 2 of the NGI, the amount of particles deposited at this stage increased 4-fold from 4.8 ± 0.7% to 19.5 ± 3.3%. These Trojan particles were highly sensitive to the magnetic field and their deposition characteristics changed in the presence compared to the absence of the magnet. The authors suggested that, if loaded with a pharmaceutical active ingredient, these particles would be useful for treating localised lung disease such as cancer nodules or bacterial infectious foci.

McBride et al. [95] also prepared magnetically responsive prepared SPION-loaded Trojan microparticles by spray drying. They referred to their formulation as a dry powder nano-in-microparticles (NIMs) system. The NIMs were prepared by spray drying a suspension of lactose, doxorubicin and Fe_3O_4 SPIONs. TEM and focussed ion beam-SEM micrographs demonstrated the porous nature of NIMs, and the surface localisation of SPIONs. NIMs deposition and retention near a magnetic field was performed using a proof-of-concept cylindrical tube to mimic the conducting airway deposition. This *in vitro* tracheal mimic study demonstrated more than twice the spatial deposition and retention of NIMs, compared to a liquid suspension, in regions under the influence of a strong magnetic gradient.

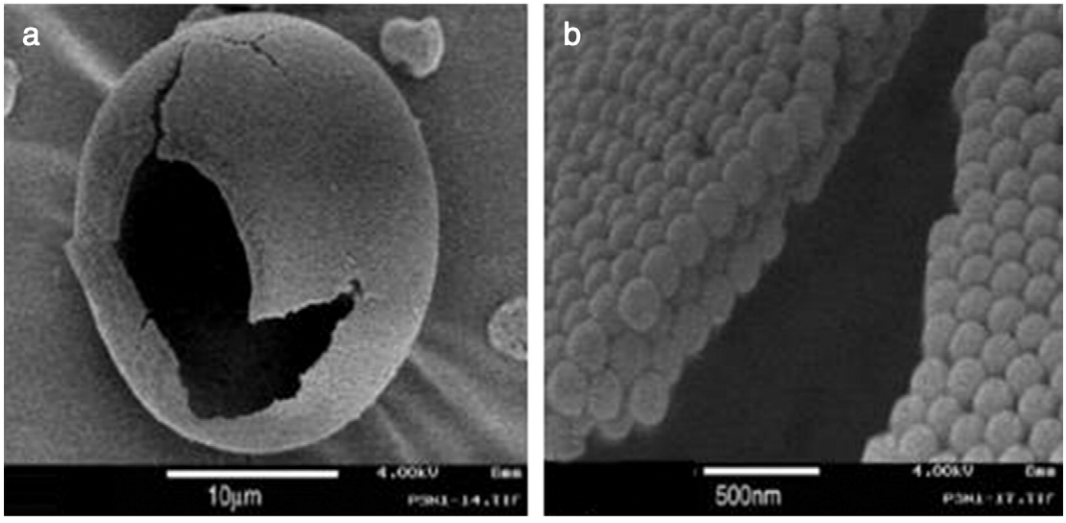

Fig. 9. Polystyrene-DPPC Trojan particles: (a) a typical hollow sphere Trojan particles observed from the spray drying of a solution of polystyrene nanoparticles (170 nm), (b) a magnified view of the particle surface in (a) (from [38] with permission).

Table 1
Summary of excipients used or with potential for use in dry powder formulations for pulmonary delivery. (Expanded from [6]).

Excipient	Function	Status
Amino acids: leucine, glycine	Improved aerosol efficiency/coating/buffering agent	Endogenous substance but no data on lung toxicity [150,151] Proven *in vitro* safety in lung cell line [148] Approved by FDA for injectables Approved DPI product: Exubera®
Ammonium carbonate	Blowing agent	Promising excipient [84]
Calcium chloride	Stabilising agent	Approved: TOBI® Podhaler
Chitosan and by-products	Controlled release	Biocompatible and biodegradable [152–155] Low or non-existent toxicity *in vitro* and *in vivo* [156–163] FDA GRAS[a]
Citric acid	Absorption enhancer	FDA GRAS[a] Promising excipient [164,165] Approved by FDA for injectables
Dextran (neutral charge)	Particle matrix/stabilising agent	Proven lung safety in animal studies [166,167] FDA GRAS[a]
FDKP (fumaryl diketopiperazine) and FDKP salt	Carrier/particle matrix	Afrezza® (MannKind Corporation) under clinical trials
Fluoralkanes	Blowing agent	Approved: in PulmoSphere™ technology-TOBI® Podhaler
Glucose	Carrier	Approved in Bronchodual® (ipratropium and fenoterol combination product)
Glycerol behanate (Compritol®)	Particle matrix	Good biocompatibility and proven lung safety [168,169]
Hyaluronic acid	Controlled release	FDA approved for injectables Promising excipient and biocompatible [170,171]
Hydroxypropyl-β-cyclodextrin	Absorption enhancer/stabilising agent	Promising results [54,172–174] FDA approved for injectables
Lactose	Carrier/coating	Approved (several products)
Lipids: phosphatidylcholine (PC) Dipalmitoylphosphatidylcholine (DMPC) Dipalmitoylphosphatidylcholine (DPPC) Distearoylglycerophosphocholine (DSPC) Cholesterol Tristearin	Particle matrix/coating/surfactant/absorption enhancer	Approved in TOBI® Podhaler™ biocompatible and biodegradable [175–177] Proven lung safety [178]
Mannitol	Carrier/particle matrix/stabilising agent	Approved in Exubera® and Bronchitol® FDA GRAS[a]
Magnesium stearate	Protection from moisture	Approved in SkyeProtect®, Seebri Breezhaler®, Foradil®, Certihaler®
Linear and branched polyethylene glycol (PEG)	Stabilising agent	Promising excipient [179–182] FDA approved for inhalation
Perflubron	Particle matrix	Approved (TOBI® Podhaler™)
PLA, PGA, and PLGA	Particle matrix/stabilising agent	PLA FDA approved for injectables Promising excipients [183,184]
Polaxamer	Surfactant/particle matrix	Good biocompatibility and proved lung safety [67,168,169,185]
Raffinose	Particle matrix/stabilising agent	Promising excipient for peptide and protein delivery [87,88,186,187]
Sodium citrate	Buffering agent/stabilising agent	Approved: Exubera® FDA GRAS[a]
Sucrose	Stabilising agent	Promising excipient for peptide and protein delivery [172,188,189] FDA GRAS[a]
Sulfuric acid	pH adjustment	Approved in TOBI® Podhaler™
Trehalose	Particle matrix/stabilising agent	Promising excipient for peptide and protein delivery [186,190–193]

[a] FDA GRAS — FDA food substance generally recognised as safe.

2.9. Adsorption/coacervation particle formation

An adsorption/coacervation technique was employed to produce sodium cromoglycate treated with a range of fatty acids crystals [102]. As the powders obtained were characterised by a variety of particle sizes, shapes and aggregation characteristics, the main aim of the study was to assess the impact of particulate characteristics on the quantity of emitted aerosolised doses and fine particle fractions *in vitro* (using Rotahaler as a DPI) from those powders. The lauric and stearic acid treatments led to an increase in the FPFs. The lauric acid formulation appeared to have altered deposition mainly by changing the particle morphology as the particles were more elongated compared to the untreated sample. The particles based on stearic acid had altered particle shape to a smaller degree than the lauric acid particulates but had even better FPFs due to reduced interparticulate interactions

3 . Excipients for DPI formulations

Many DPI formulations that are carrier-free comprise API co-formulated with a range of excipients to produce composite particles designed for efficient delivery from the DPI device and deposition into the pulmonary regions.

An excipient is a pharmacologically inactive component of a finished pharmaceutical product. Its use is directed to improve the physical or chemical stability, the mechanical and/or pharmaceutical properties of the active pharmaceutical ingredient, when producing a drug dosage form. The choice of an excipient is based on the function(s), which it is supposed to take within the formulation and on the target of delivery (IV, oral, transdermal, pulmonary delivery).

The use and source of excipients are regulated by the authority which will approve the pharmaceutical product, *e.g.* the Food and Drug Administration (FDA) and the European Medicines Agency (EMA). These authorities issue general regulatory guidance [103–106], however a specific listing of excipients to be used in a particular pharmaceutical form, such as dry powder inhalers, does not exist. Nevertheless, the FDA has a list of materials/substances that are generally recognised as safe (GRAS substances). The choice of excipients is generally made based on this list or on its use in previously approved products and, it is a requirement that the manufacturer of a new dosage form submits full detailed information (production, safety, toxicology) when applying for approval of its new product. The smaller the number and quantities of excipients

incorporated in a formulation, the better in terms of regulatory approval. Table 1 presents a summary of excipients currently used in dry powder formulations for inhalation, based on approved marketed products and studies on demonstration of safe-use of excipients intended for inhalation.

4 . Dry powder inhaler devices suitable for carrier-free formulations

Over the past 40 years, dry powder inhalers have been marketed with various devices and formulations [32,107–109]. The dry powder platform is characterised by presenting the medication to the patient as a dry powder administered using a device specifically designed for that formulation. In general, the inhalers employ the patient's inspiratory flow as the means of dispersion and entrainment of the aerosol into the lungs, the so called breath-actuated devices; however nowadays passive devices have been produced were the device itself produces the aerosol disregarding the patient flow [32,108,110,111].

The DPI device should assist in the generation of very fine particulates of medication in a way that enables them to avoid the impaction barriers that normally operate in the lung to prevent the ingress of potentially harmful particles. More recently there is an increasing trend to focus on optimising the combination of powder technology, device, and combination of powder-device technology to improve the aerosol generation. In general, inhaler design, particularly the geometry of the mouthpiece, is critical for patients to produce sufficient airflow to lift the drug from the dose chamber or capsule, break up the agglomerates in a turbulent airstream, and deliver a dose to the lungs as therapeutically effective fine particles. Each inhaler will present a resistance to airflow (measured as the square root of the pressure drop across the device divided by the flow rate through the device), with current designs having specific resistance values ranging from about 0.02 to 0.2 ($(cm\ H_2O)^{1/2}$/LPM) [112,113]. In order to produce a fine powder

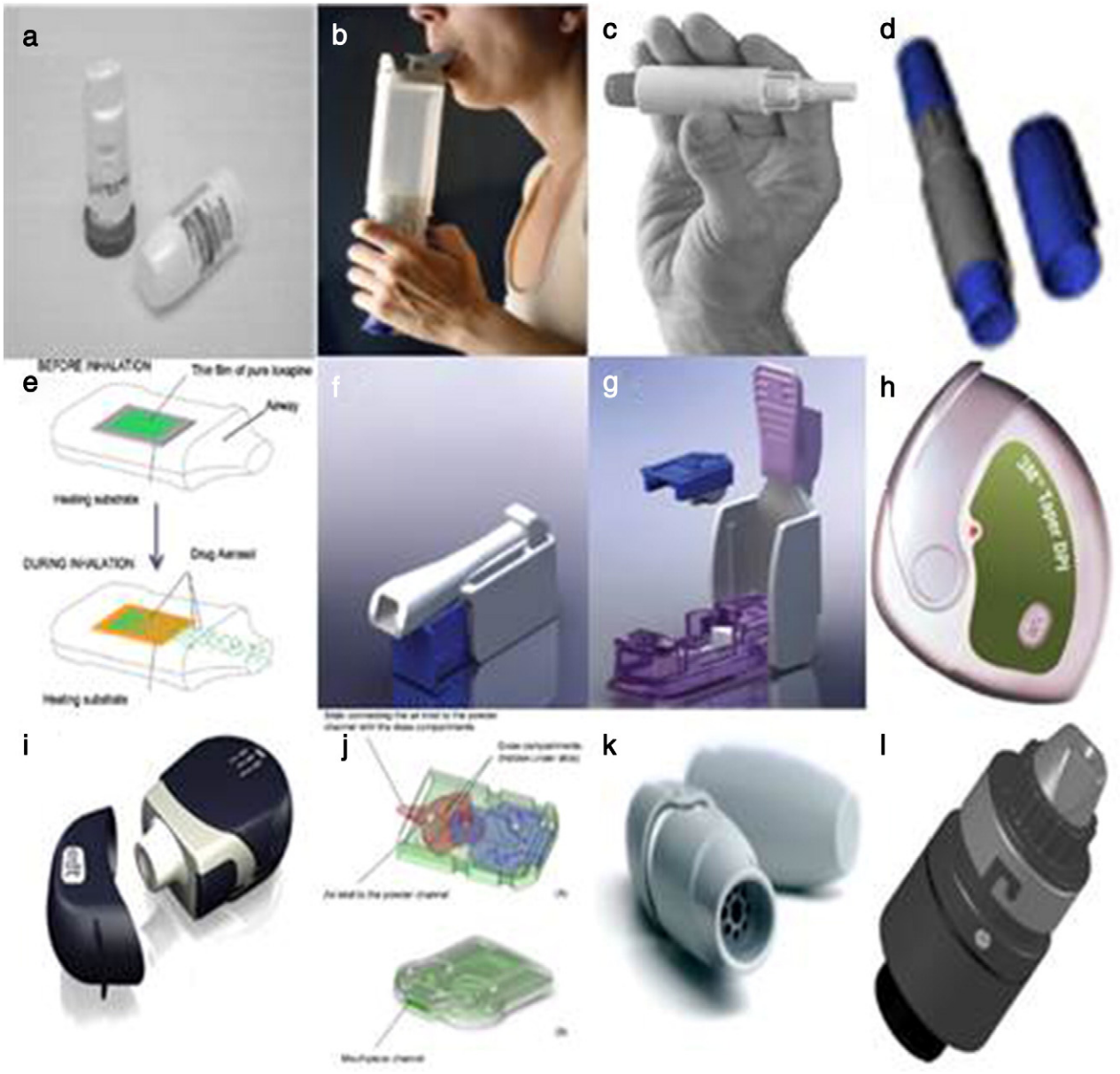

Fig. 10. DPI devices: (a) Turbuhaler™/Turbohaler™ (from [114] with permission), (b) Exubera® (from [146] with permission), (c) Podhaler™ (from [147] with permission), (d) Turbospin ™ (from [148] with permission), (e) Staccato® (from [149] with permission), (f) Cricket™ (from [130] with permission), (g) Dreamboat™ (from [130] with permission), (h) 3 M Taper DPI ™ (from [131] with permission), (i) MicroDose DPI (from [133] with permission) (j), Twincer™ (from [137] with permission), (K) ARCUS® inhaler (from Civitas Therapeutics with permission) (l) DPI — The University Of Western Ontario (from [143] with permission).

aerosol with increased delivery to the lung, a DPI that is characterised as having a low resistance requires an inspiratory flow of >90 L/min, a medium-resistance DPI requires 50–60 L/min, and a high resistance DPI requires <50 L/min [113].

The ideal DPI system should include most or all of the following attributes [106,109]: simple and comfortable to use; compact and economical to produce; multi-dose system; a reproducible emitted dose over a wide range of inspiratory flow rates and throughout the inhalers life span; highly reproducible fine particle dosing; physically and chemically stable powder; minimal extrapulmonary loss of drug (low oropharyngeal deposition, low device retention, and low exhaled loss); powder protected from external environment and can be used in all climates and protected from moist exhaled air; overdose protection and indicate number of doses delivered and/or remaining: suitability for a wide range of drugs and doses.

DPIs can be "single-dose" or "multi-dose" (multiple unit dose and multi-dose), depending on the design of the powder reservoir and metering components. In "single-dose" devices, individual doses are provided, and usually have to be loaded into the inhaler before use, however they present a disadvantage since patient agility to load the drug is required. "Multiple unit dose" inhalers contain a number of individually packaged doses, either as multiple gelatin capsules or in blisters. In "multi-dose" devices, drug is stored in a bulk powder reservoir, from which individual doses are metered [112].

Numerous DPIs have been marketed containing lactose as a drug carrier. As the scope of this review is carrier-free delivery systems, we now present a short review of the devices marketed, upcoming devices and devices under study for such formulations. The design of such devices is driven by the previously referred limitations of DPIs such as flow rate dependency for breath-actuated devices and effective powder de-agglomeration [109].

4.1. Marketed devices

4.1.1. Turbohaler®

The Turbohaler® (referred to as Turbuhaler® in some countries) (Fig. 10) is manufactured by AstraZeneca and was one of the first DPIs to dispense doses metered from a reservoir inside the inhaler [5,112]. The device is made up of 13 plastic components and a steel spring, with a reservoir that may contain 50, 100 or 200 doses of active drug/API. The drug-loading system ensures that each dose is metered accurately regardless of how much powder remains in the reservoir and it is not possible for the patient to accidently inhale an overdose [114]. A dose indicator tells the patient when there are 20 or fewer doses remaining [112,114]. A single dose is loaded when the grip at the base is fully twisted in one direction and back again. This action fills a cluster of precisely machined conical holes in a rotating dosing disc, and scrapers then remove any surplus drug as the disc passes beneath them, ensuring accurate dosing. Inhalation through the mouthpiece forces air through the holes in the dosing disc, lifting the powder through the inhalation channel and into the deaggregation zone. This consists of two spiral channels in the mouthpieces which are aerodynamically designed to create a turbulent flow to disperse the powdered drug. As the efficiency of drug deaggregation is airflow dependent, extra air is admitted just below the mouthpiece, reducing the pressure drop and increasing linear velocity. The device presents an airflow resistance of approximately $R = 0.11\ (\text{cm}\ H_2O)^{½}/\text{LPM}$. The Turbohaler® has a protective cover that screws tightly onto the base, which contains desiccant, intended to keep the interior dry for at least 200 open/close cycles [5,114,115] It was designed for small quantities (<1 mg) of drug per activation, without the use of any carrier compound [5]. The loaded drug formulation comprises soft aggregates, with a diameter of approximately 0.5 mm, of micronised API formed by spheronisation [5,112]. The Turbohaler® emitted dose is dependent on the inspiratory flow rate ranging from 60 to 90% (low to high inspiratory flow rate) [112].

The Turbohaler® has been approved for the drugs budesonide (Pulmicort®, Spirocort®), formoterol (Oxis®), terbutaline (Aerodura®, Bricanyl®) and a combination of budesonide and formoterol (Symbicort®).

4.1.2. Exubera®

Exubera® (Fig. 10), insulin inhalation powder, was a system developed by Nektar Therapeutics consisting of two components: the drug product, a spray dried insulin powder in unit dose blisters and a reusable pulmonary inhaler, a medical device, formed by three subsystems: base (air pump and valves), TransJector (small jets), and chamber/mouthpiece. The DPI was a power assisted inhalation device (patient flow independent) [36]. The device design is purely mechanical, using patient-generated compressed air as the energy source to deliver small amounts of cohesive powder (1–10 mg) [36,104,116]. Upon actuation, a sonic discharge of air from the base through the TransJector into the chamber reproducibly extracts, de-agglomerates, and disperses the inhalation powder into a respirable aerosol. A clear holding (spacer-type) chamber allows for patient feedback *via* dose visualisation, and separates powder dispersal from the inspiratory effort [36,104,116].

Exubera® was approved by the American and European Drug Agencies (FDA and EMA (previously EMEA)) in early 2006. However, in October 2007, Pfizer announced Exubera's removal from the market due to failure in gaining market acceptance [117].

4.1.3 . Podhaler™

The Podhaler™ (Novartis T-326 inhaler) (Fig. 10) is a portable, capsule-based, single-dose, multiuse DPI, which is mechanical and does not require an external power source or electronics (breath-actuated). A capsule containing the active drug/API is loaded into the device by removing the mouthpiece and inserting the capsule into the chamber. The mouthpiece is screwed back onto the body, the button is depressed to pierce the capsule, and the patient inhales through the mouthpiece. During inspiration, the capsule rotates rapidly in the chamber, which causes the active drug/API to be emptied from the capsule. The Podhaler™ has relatively low airflow resistance (approximately $R = 0.08\ (\text{cm}\ H_2O)^{½}/\text{LPM}$) to allow patients to generate high airflow rates and produce reliable dose delivery [115,118]. Studies estimated that a patient could essentially empty a capsule with a single 1.0 L inhalation at a 40 L/min flow rate or with two 0.6 L inhalations using a 30 L/min flow rate, resulting in an emitted dose of 90% [118]. The device is stored in a case between use to prevent moisture uptake by residual powder in the device [115].

The Podhaler™ is marketed as TOBI® Podhaler™ a tobramycin formulation using the PulmoSphere® technology indicated for infections caused by *P. aeruginosa* in patients with cystic fibrosis.

More recently, Bayer has launched its clinical trials phase III of Respire® a ciprofloxacin DPI also using the PulmoSphere® technology and the T-326 inhaler, for patients with non-cystic fibrosis bronchiectasis (NCFB) [119,120].

4.1.4 . Turbospin™

Turbospin™ (Fig. 10) is a single-dose, multiuse DPI designed and patented by PH&T for effective drug delivery to the lungs. Its shape resembles a pen, being composed of a cap and a device for inhalation. The cap protects the apparatus from the external environment. The device is made of plastic (medical grade polypropylene) and consists of the mouthpiece and the body, which encloses the pulverisation chamber and the piercing apparatus for the capsule. The capsule is vertically inserted in the pulverisation chamber and pierced by the needles at the bottom. Air is drawn through the aerodynamically designed chamber slits by inspiration, creating turbulence that shakes and twists the capsule, facilitating its emptying. Two versions of the inhaler have been developed: the original, suitable for housing a size 2 capsule; and a more

recent device that accommodates a size 3 capsule. The drug in dry powder form is protected by the blistered capsule [121,122].

Turbospin is currently being marketed as Colobreathe® by Forest Laboratories UK Ltd., which contains excipient-free micronised colistimethate sodium (colistin salt form) an antibiotic against *P. aeruginosa* an infectious agent that commonly affect cystic fibrosis patients.

4.1.5 . Staccato®

Staccato® device (Fig. 10) is single-dose and single-use inhaler designed by Alexza Pharmaceuticals, based on the possibility of powder sublimation. This is achieved by rapidly heating a thin film of active drug/API. The heating process is very quick, less than half a second, in order to prevent thermal decomposition of the API. It is triggered by the patient's inhalation. After sublimation, the API cools rapidly in air, condensing into aerosol particles of one to three μm in size, that are drawn into the patient's mouth and into the lungs, throughout inhalation. The emitted dose is ~90% of the coated drug and consistent and independent of the patient's breathing pattern, as the device presents a valve that controls the airflow. Hence, a patient simply removes an inhaler from its packaging, places the device to his or her lips, and takes a deep breath [123,124].

The Staccato® device may not correspond to what one might normally consider to be a DPI; still it is a device that contains API in a powder form (solid state), as for other DPIs, and that requires breath activation for powder dispersion (sublimation in this case) and delivery into the lungs, in the same manner as for other DPI devices described in this review.

The Staccato® is marketed as Adasuve™ (loxepine) an antipsychotic indicated for the acute treatment of agitation associated with schizophrenia or bipolar I disorder in adults. Additionally the device is being studied for the delivery of other drugs such as: fentanyl, zalepton, alprazolam and prochlorperazine [123].

A multiple dose *Staccato®* is also under development, consisting of a reusable controller and a disposable dose cartridge, which contains up to 25 separate metal substrates coated with the drug [124].

4.2 . Upcoming devices

4.2.1 . ARCUS® inhaler

The ARCUS® inhaler by Civitas Therapeutics (MA, USA) a spin-out company of Alkermes, (MA, USA), was once known as the AIR® inhaler (Fig. 10). It is a small, simple, portable, capsule-based, breath-actuated device that allows the delivery of single or multi-doses of an API/formulation using the large porous particles technology [125,126]. The device consists of two portions: a cylindrical chamber with multiple vents and a U-shape staple (puncturing mechanism); and a second portion consisting of the mouth piece and device body. Upon loading of a capsule into the chamber, the patient activates the puncturing mechanism, creating two holes in the capsule; once breath-activated the powder is dispersed in the chamber (due to vents and capsule spin motion), and inhaled by the patient. The inhalation device is configured to a have a resistance of at most 0.28 $(\text{cm } H_2O)^{1/2}$ L/min, allowing its use at different inspiratory flow rates and inhalation volumes [126–128].

The inhaler is currently being used in Civitas' lead programme, CVT-301, an on-demand therapy for treating OFF episodes associated with Parkinson's disease [129].

4.2.2 . Cricket™ and Dreamboat™

MannKind Corporation has developed two devices as part of their dry powder — device combination technology: a single-use, disposable device called Cricket™ (Fig. 10), and a reusable (15 days of use) device called Dreamboat™ (Fig. 10) [130]. The latter is currently used on their Afrezza® (see Section 2.5) inhaled dry powder insulin product which is in development.

To inhale a dose using the Dreamboat™, the patient opens the device, inserts a unit dose plastic cartridge containing the Technosphere ™ powder formulation, closes the device, and inhales the powder through the mouthpiece in a single breath. After dosing, the patient opens the device and then removes and discards the emptied cartridge. Alternatively, to use the Cricket™, the patient removes the pre-loaded, single-use device from the package, activates by depressing the purple button, and inhales the powder through the mouthpiece in a single breath. For both devices the powder is expelled from the device by the patient's inhalation [44].

Both devices present a common flow path: as a patient inhales, two flow inlet streams converge simultaneously. The first inlet stream lifts the powder from a containment region to fluidise it and deliver it into a second by-pass inlet stream. The intersection of these two inlet streams de-agglomerates the fluidised powder, which then travels down a mouthpiece outlet and into the mouth. The powder dispersion occurs rapidly and early in the patient's inhalation manoeuvre [130]. In addition, the inhalers utilise a high resistance design enabling low in-use flow rates that reduce powder deposition in the throat and promote deep lung powder deposition for ease of patient use [130].

4.2.3. 3M Taper™ DPI

The 3M Taper™ DPI, produced by 3M Drug Delivery Systems, is a multi-dose inhaler characterised by presenting the active drug/API on a microstructured carrier tape (MCT) (Fig. 10). The inhaler uses 3M micro-replication and extrusion technology to create a “dimpled” tape upon which one or more active drug/API are coated, enabling it to provide up to 120 pre-metered doses. The dimple design allows the use of API only, eliminating the need for lactose; API loading is based on a balance between API retention in the dimples upon manufacturing and API release upon dosing. The cohesive nature of the API (van der Waals forces, interlocking mechanism, *etc.*) is vital for this process. The amount of API delivered with each dose is determined by the number of dimples on the tape, the volume of each dimple, and the density of API powder packed into the dimples; therefore, individual doses in the range from 100 μg to 1 mg are possible [131].

The device is small and compact and intuitive requiring only opening the device, where fixed length of the MCT is presented into the dosing zone within the device; inhaling, the air flow releases an impactor that strikes the tape and releases API into the airstream, with further de-agglomeration of particles as they pass through the device; and closing. The device also features a ready indicator that changes from green to red and makes an audible click; and a large, easy to read dose counter [131].

The 3M Taper™ DPI is not currently in the market, however its technology has recently been acquired by Adamis Pharmaceuticals for future use in asthma and chronic obstructive pulmonary disease treatment [132].

4.2.4 . MicroDose DPI

MicroDose Therapeutx, Inc. has developed an electronic dry powder inhaler which utilises a piezo vibrator to deaggregate and aerosolise drug powders packaged in either moisture-resistant aluminium or plastic blisters (Fig. 10). The device can be designed to be reusable, accepting either single-dose or multi-unit dose disposable cartridges. It is operated in four steps: open cap; advance dose; inhale; close cap. Blisters are pierced with small needles prior to dosing to create openings into the flow channel of the device. Through breath activation (inhalation), the piezo transducer converts electrical energy to mechanical energy (vibration), which is transferred through the blister into the powder, creating an air pressure (high velocity air jets) at the blister holes, levitating and dispersing the powder. The fine powder emitted from the blister is entrained in the patient's inspiratory airflow and inhaled into the lungs. Because the piezo vibrator generates the energy needed for powder aerolisation, inspiratory flow dependency is eliminated. MicroDose DPI can be used with different drug compounds and

formulations, *via* adjustment of the piezo transducer drive circuitry in order to optimise it for delivering a new compound. The device is capable of an emitted dose above 90%, with high fine particle fractions (50 to 95% as a percentage of emitted dose) [133].

MicroDose Therapeutx, Inc. and Moerae Matrix, Inc. have agreed to develop a DPI product of Moerae's novel MK2 inhibitor, MMI-0100, for the treatment of idiopathic pulmonary fibrosis (IPF) [134]. Clinical Trials are also under way in a partnership with the U.S. Department of Defense Chemical Biological Medical Systems and the University of Pittsburgh Medical Center for the delivery of atropine as a systemic and pulmonary treatment for the extended recovery period after chemical weapons exposure, with a phase 1 pilot trial already completed [135].

4.3 . Devices under development

4.3.1. Twincer™

The Twincer™ is a disposable DPI developed at the University of Groningen in the Netherlands (Fig. 10), for the delivery of high drug doses up to 60 mg. It is constituted by three plate-like parts presenting various projections and depressions (which constitute the air flow passages), and a blister chamber containing the active drug/API to be delivered [136,137]. The blister has a long cover foil which, by pulling, connects the powder channel and the inlet to the blister chamber. Air passing through the powder channel during inhalation entrains the powder from the blister; this powder flow is then divided between two parallel classifiers, which are circular depressions in the bottom plate of the inhaler, where by inertial and shear forces the API agglomerates are de-agglomerated and consequently delivered to the patient [137,138].

The device was designed and studied for colistin [137], and has also been used in studies for pulmonary delivery of peptide and proteins, and vaccines [139,140]; it is manufactured by Indes (Netherlands) for use in small clinical trials such as colistin delivery for cystic fibrosis [141]. The University of Groningen continues on their research, optimising the Twincer™ and adjusting its use for different formulations.

4.3.2 . Dry powder inhaler — the University Of Western Ontario

The University of Ontario has developed a novel multi-dose dry powder inhaler to deliver very small dosages of API powders into the lungs (100 μg–500 μg) (Fig. 10) [142]. The inhaler is formed by a rotating multi-dose disc with pure drug pre-metered in small pocket holes drilled through the disc, which is placed between the air tubule and compress chamber, leaving only one drug pocket (which volume determines the dose) in the air passage for a given dose; up to 60 doses can be held on the disc [143]. A two air flow design is applied to produce complete dispersion of API powder with the break-up of most agglomerates of powder: primary airflow — the patient pushes a bottom button, producing compressed air that flows through the drug pocket, carrying drug powder along the air tubule until ejecting the powder out mouthpiece; secondary air flow — perpendicular to primary air flow providing an additional shear flow, and assisting in entraining the fluidized powder into the primary air flow for complete de-agglomeration and aerosolisation of the API powder [142–144]. After one dose is delivered, the disc can be rotated to set a new dose in the air passage for the next administration [143]. The emitted dose from the inhaler was found to vary between 88% and 92% for phenylalanine and insulin powders, with corresponding FPF of 65% and 69% [143].

5 . Conclusion

Research on carrier-free DPI products dates back to the mid to late 90s, however it is only in recent years that products based on carrier-free formulations have reached the marketplace. In parallel to formulation development, new inhaler designs allow for improved deaggregation and dispersion of dry powders. The combination of powders designed, by sophisticated particle engineering or novel formulation approaches, to have reduced cohesiveness and improved flowability and dispersion characteristics, together with efficient DPI devices, opens up opportunities for more carrier-free products to be commercialised.

The omission of a carrier, such as lactose, from the product obviates the need for control of the potentially variable characteristics associated with the carrier and the quality and uniformity of the powder blend. Carrier-free formulations have been shown to be as effective or, in many cases, more effective than traditional carrier-based products in terms of their aerosolisation and deposition characteristics and their efficacy *in vivo*. We can expect to see the number of marketed carrier-free dry powder inhalation products increasing in the coming years.

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