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A view on the less-than-rational development of drug delivery systems – The example of dry powder inhalers

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ABSTRACT

This review is about the meandering course of science. It uses the research on, and development of, dry powder inhalations (DPIs) as a case study. It suggests that the influences can be classified as bottom-up (reductionist, specific) and top-down (whole-system – gestalt). Based on information in the public domain, it seems that DPI research has taken a meandering course being influenced by historical and cultural beliefs, communication and debate, serendipity and chance comment and regulation. It has also been strongly influenced by the availability of highly sophisticated equipment which has been used to characterize particles and their interactions, as well as their deposition in the lung. DPI research has been influenced by closely related (e.g. oral drug delivery) or distantly related (mineralogy, industrial hygiene) disciplines and now it influences other disciplines. Sometimes the time period for inter-disciplinary knowledge transfer has been surprisingly long. The primary aim (or outcome) of DPI research is improved healthcare for people through efficient pulmonary drug delivery. A fundamental aim is improved mechanistic understandings of the behaviour of particles in DPIs to give increased predictive ability.

1. Introduction

This review is about dry powder inhalers (DPIs). Its aim is not to critically review the recent literature on the subject with a view to understanding the current state of the field and its future directions. There are many useful review articles which do this [1–4]. Rather, the aim is to consider the factors which have influenced the meandering course of research and development of DPI-science and technology. What were the stimuli and enabling factors which caused it to take one direction rather than another? This is somewhat akin to a systems approach to understanding a complex biological system. The system in which scientists and engineers work is equally complex with feedforward and feedback mechanisms, there are influences which are closely linked to an immediate research action (e.g., grant funding) and other influences which are widely separated in time and intellectual space (e.g., fundamental particle research). There are apparently trivial events (e.g., a chance discussion at a conference) which initiate research collaborations and new research directions and major, apparently unrelated events (e.g., hole in the ozone layer), which have unforeseen influences (e.g., regulatory bans on CFCs leading to reformulation with HFAs and a shift to DPIs).

Two extreme classifications of the influential drivers of a field are possible: bottom-up (specific) and top-down (gestalt). Bottom-up factors include: developments in fundamental science being applied upwards; novel equipment being applied upwards. This approach is far easier to describe and it is probably operative at the fine scale. The top-down approach suggests the direction of a field is influenced by the global whole, the gestalt. Thus, a field is influenced by public drive or actions of pressure group, public fears (e.g., of cancer), politics as well as enabling science and technologies. When thinking about such influences, the mnemonic PESTLE, apposite for drug delivery, encapsulates the spectrum of influencing factors: political, economic, social, technological, legal and environmental. Although the role of such influences may not be apparent before the fact, a post-mortem commentary on the failure of Exubera®, a highly anticipated inhaled insulin, is a good case-study [5]. It discusses how the viewpoints of patients, diabetologists, scientists, pharmaceutical industry, health-care

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payers, and politicians influenced, or perhaps should have influenced, the direction of the research on inhaled insulin.

Before considering some of the factors which have influenced the direction of research on DPIs we briefly summarize some history.

2. A brief overview of dry powder inhalation

Records and artifacts from Egyptian, Chinese, Indian, Greek and other ancient civilizations show that inhalation therapy has been used for thousands of years. Leaves, resins and other crude drugs were placed on hot bricks, or into boiling water or smoking pipes, to release volatile components for inhalation by asthmatics or for other lung conditions [6]. It is therefore reasonable to ask if smoking was the earliest form of powder inhalation. Fresh mainstream cigarette smoke is an aerosol of solid and liquid particles in a chemically complex gas. The average diameter of smoke particles is about 0.2 μm but they grow rapidly (5 s) due to coagulation and absorption of water to particles with mean diameter of ~0.7 μm [7]. Recent studies have shown the presence of nanoparticles (<50 nm) as well [8]. So it would seem that smoking was the earliest method of inhaling particles for therapeutic or social reasons, although the particles were not engineered for optimal delivery to the lung.

An example of the first rationally considered delivery of particles to the lungs is that of Dr Chambers who loaded lycopodium spores with copper sulphate and silver nitrate by soaking the spores in a saturated solution of these salts. The loaded spores were then dried and powdered [6]. Lycopodium spores have a geometric diameter of about 30 μm and a density of about 1.2 g cm^{-3} so even if Chambers managed to reduce the wet mass to individual spores, his engineered particles were still larger than the optimal (5 μm) for a powder of the above density.

The efficacy of the modern DPI depends on the optimal combination of the dry powder formulation and the device, a fact not appreciated in the original devices. The Newton dry powder inhaler (1864) a box the size of a mantle clock, was used for inhaling potassium chlorate powder. The powder was dispersed by the patient's winding a handle to drive feather beaters, while inhaling through an orifice in the box [6]. The late 1940s saw the development of passive DPIs in which the patient's inspiratory air flow was used to drive dispersion of the powder. In the following decades more sophisticated passive DPIs were designed as well as active devices (Fig. 1) and in 2008 it was reported that there were more than 20 DPI devices on the market and >25 in development [9]. From a pragmatic perspective, some of the development of the DPI has been driven by the desire to create a device that can deliver drug effectively to the lungs but also to create novel and innovative (i.e., patentable) intellectual property which does not infringe existing designs. This has led to a plethora of designs in the patent literature which use different powder dispersing strategies and de-agglomeration principles [10].

A modern DPI has three components: a powder formulation; a metering system (unit, multiunit and reservoir); an aerosolisation mechanism. The latter requires energy input into the powder bed by mechanical (vibration, impact, compressed air, impellers) and electrical methods. Pulmonary drug delivery attempts to achieve the aims of drug delivery in general: deliver the drug at the appropriate dose, rate, site and time. Consequently, the rational design of DPIs depends on understanding:

- where a drug should be delivered in the respiratory system and how deposition is influenced by the physicochemical properties of the drug particles, breathing patterns and pathology
- aerosolisation, and how it is influenced by interaction between drug particles and excipients, and the design of the device. Since interactions between drug particles and between drug particles and excipients are dependent on the surface chemistry and physical properties of the particles, predictive ability requires that these phenomena are understood at more fundamental levels.

Developments in DPIs have therefore required integration of diverse knowledge, skills, techniques, and materials. The pharmaceutical sciences have made great strides in the last 50 years which have contributed in major ways to healthcare. These contributions have been considered in some detail [11] but one could be left with the impression that the developments have been logical and rational, as might be expected in good science. However, it is our contention that at least in the field of DPIs, progress has been influenced by chance, opportunity and need, not necessarily scientific rationality. There has been slow application of fundamental scientific principles (JKR theory, DMV theory and work of John Hersey, published in the early to mid-1970s) to powders for inhalation. Based on the published literature, these scientific principles were not applied to powders for inhalation until the late 1980s even though modern DPIs were available from the 1970s.

We now consider some of the factors which have influenced the development of DPIs.

3. Historical influences in overview

Our beliefs and thinking (and biases) about lung delivery are not only influenced by current science but also by 'inherited' beliefs, which might or might not have a scientific basis. When confronted with new challenges or in new learning environments, people, and this includes scientists, draw on their accumulated science and non-science to learn and to negotiate the challenges with creativity.

Thinking on inhalation therapy is influenced by memes [12] which have their genesis in the ancient cultures. For example, the idea of delivery to the site of the problem is an old one dating back thousands of years to ancient civilizations [6]. Many scientists will have memories of having their head covered with a towel while they inhaled vapours from a basin filled with hot water and inhalation. So the idea of local delivery for lung conditions is an ancient and continuing idea. It was propagated by Stern in 1778, who having noticed the low efficacy of orally administered medicines, published a pamphlet entitled "Medical Advice to the Consumptive and Asthmatic People of England". In it he advises that the only possible way of applying medicines directly to the lungs, is through the windpipe." (http://www.inhalatorium.com/page133.html).

Recently, pulmonary delivery scientists have been turning their attention to the treatment of pulmonary tuberculosis by delivery of antibiotics [13]. This too has a long history in that the treatment of consumption (TB) by inhalation of arsenic was advocated by Rhazes, a Baghdad physician around 900 AD and an inhalation device for delivery of balsam vapours was described in a publication in 1654 [6].

Sometimes history sends contradictory messages. The idea of systemic delivery via the lungs, something we have come to accept as reasonable, was not always seen this way. The Medical News section of The Lancet reported in 1848: "After homoeopathy and hydropathy, we have now aeropathy,—a, new piece of charlatanism, by which Dr. Chaponnier introduces all therapeutical agents into the system, through the respiratory organs, in the form of vapour" [14]. However, given the long history of tobacco and opium smoking with obvious systemic effects, it is not surprising that the idea for systemic delivery via the lungs continued. Insulin was given in this way as early as 1924 and was shown to lower blood glucose in 1925 [6] and when the biotechnology industry was being challenged to find alternatives to the oral and parenteral

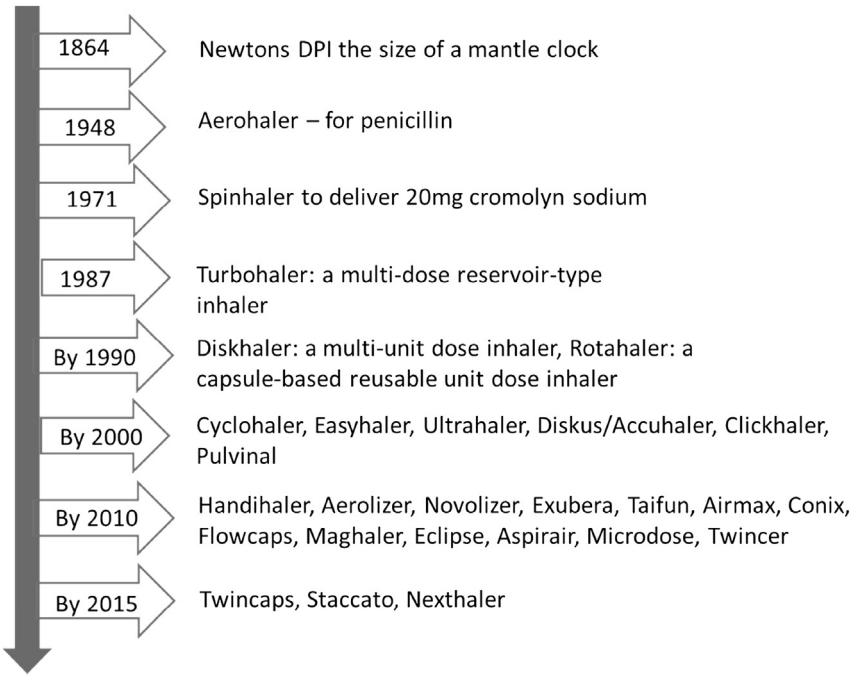

Fig. 1. Some developments in dry powder inhaler devices.

routes in the 1990s, insulin was again a molecule of interest. Just as development of a new product may be influenced by a complex mosaic of factors, the demise of Exubera® only one year after its launch has been attributed to formulation and device issues, apparent safety considerations, marketing pricing and sales inadequacies [2]. Importantly, the learnings on inhaled insulin now become the history to encourage, discourage and inform research on the pulmonary delivery of other therapeutic proteins and peptides, as well as insulin itself. In 2014, the FDA approved Afrezza® a rapid-acting inhaled insulin.

4. The role of dialogue and communication among disciplines

In an era in which we take immediate world-wide communication for granted, email constantly demands our attention, when we have numerous journals in which to publish and to read, and a surfeit of conferences from which to choose, there is a danger that there is too much opportunity for dialogue and not enough time to do the research to talk about. This was not always the case.

The specialization and professionalization of science was accompanied by the elevation of 'print' as the preferred means of communication of science. Prior to the mid-nineteenth century, science (natural philosophy) was a topic of genteel conversation and culture. Science was shared via public lectures, dinner conversation, in the salons and coffee houses, magazines and newspapers. In the 18th century, Oxbridge professors did not publish much but cultivated a local reputation through informal associations and high-table conversation. However, as scientists were replaced by the industrialists at genteel society's dinner tables, there was a need to create opportunity for sharing ideas. In 1879, Lord Rayleigh introduced tea breaks at the Cavendish Laboratory as a way to combine relaxation with free conversation for the hatching of new scientific ideas. His wife attended these. Anthropologists have examined the discussions of scientists and technicians in these laboratories in order to understand science in the making [15]. Such studies enrich a discipline and give some understanding of its history. Although a systematic study of such conversations in relation to the development of DPIs is a future challenge, a personal experience of one of the authors (PJS) exemplifies the long-lasting influence of conversation.

As a young pharmaceutical scientist, PS attended a presentation by the late John Hersey on ordered, interactive powder mixes. Although Hersey's application of such systems was to achieve dose uniformity in low dose oral tablets, the lecture inspired and strongly influenced PS's research career and its focus on particle interactions in DPIs.

At a discipline level, the need for dialogue and communication has dramatically increased in recent years. In an article on the evolution of drug development and clinical pharmacology in the 20th century, the authors noted the scientific expertise from many specialties, including pharmacology, toxicology, clinical medicine, pharmacokinetics, clinical pharmacology, genetics, molecular biology, biotechnology, and chemistry is now required to bring a drug into the clinic. They suggest that the degree to which these specialists communicate and cooperate during drug development determine the degree to which the process will succeed [16]. This is in line with recent research which has found that, contrary to the expectation that the quality of a research group is given by the average calibre of its individuals, in fact intra-group interactions play a dominant role, and that there is a discipline-dependent critical mass of scientists for optimal research performance [17,18].

In this age where data are measured in terabytes, scientists can be overwhelmed by its volume, variety and velocity. In 1971 it was noted that progress in science in essentially determined by the stimulating effects of accumulation and transfer of information and that those concerned with the allocation of resources for science might ask if it is possible to control the direction of science toward some desirable goals [19]. Their approach of using citation data and a Markov chain model which attempted to predict the stimulator effect of one field on another now seems crude and simplistic. The new fields of bibliometrics, scientometrics and their subfields which study clustering of information, interactive journal maps, cross-citing of one field by another, impact of a field or article,

impact of a researcher, etc reveal the importance of the gestalt on the direction and outputs of a field.

A Scopus search for 'dry powder inhal*' in the title, abstract, keyword fields resulted in 1857 research articles in the period 1978–2014 (inclusive) with a dramatic increase in publications in recent years (Fig. 2). These were published in 158 journals. Of interest is that 241 of these papers are associated with 10 scientists emphasizing the role of luminaries or leading thinkers in scientific fields. This is not to suggest that these are the 10 scientists responsible for driving dry powder inhaler products to the market. A search of the scientific literature using a strategy which targeted engineering aspects or clinical aspects of DPIs would yield different names; a search of the patent literature would yield yet another set of names. But this emphasizes the interdisciplinary nature of research and development today.

The papers were published in 23 different subject areas demonstrating the diversity of fields which influence the research and which are influenced by the research on dry powder inhalers (see Table 1).

Table 1
Subject areas in which research papers on 'dry powder inhal*' were published in the period 1978–2014. Note some papers are allocated to several fields.

Subject area	Number
Medicine	968
Pharmacology, Toxicology and Pharmaceutics	919
Biochemistry, Genetics and Molecular Biology	252
Chemistry	211
Chemical Engineering	99
Materials Science	52
Immunology and Microbiology	47
Environmental Science	42
Engineering	39
Physics and Astronomy	21
Earth and Planetary Sciences	18
Nursing	13
Social Sciences	13
Agricultural and Biological Sciences	8
Health Professions	8
Veterinary	7
Mathematics	5
Neuroscience	5
Undefined	5
Computer Science	3
Dentistry	2
Multidisciplinary	2
Economics, Econometrics and Finance	1

5. Serendipity

Serendipity is about making a discovery by chance, it is a pleasant surprise, and according to the Oxford Dictionary a discovery which is not relevant to any present need, or in which the cause is unknown. However, it is also said that serendipity depends on both chance and wisdom, that is the ability to see the relationship or usefulness of a chance observation in another area of science or application – as Pasteur is reported to have said: "chance favours the prepared mind". So perhaps serendipity is a name being given to a situation which has not been analysed in detail to understand the reason for the chance discovery. To some degree, serendipity is the opposite of "rational drug delivery" a term first used in 1976, although not in relation to pulmonary drug delivery [20].

The role of serendipity in drug discovery is well reported, penicillin being a classical example. However, examples of serendipity in drug delivery are rare. A Scopus search on 'drug' AND 'serendipity' in the Title, Abstract, Keywords fields gives 337 references from 1964 to 2014. The same search on 'drug delivery' and 'serendipity' yields a mere 13 papers, only one of which relates to delivery per se [21], and none to pulmonary drug delivery. The possible conclusions are that serendipity has not played a role in pulmonary drug delivery and scientists in this area work rationally, or they do not report serendipity, or they have not analysed the discovery, or they provide a post-hoc rational explanation which is more acceptable to referees and journal editors.

If a chance comment which leads to a new technology might be seen as a form of serendipity, then there is a famous example of serendipity in the development of inhalation technology, namely the pressurised metered dose inhaler (pMDI). Charlie Thiel and colleagues led the development of the pMDI at Riker Laboratories in the 1950's. He reported that Susie Maison, the daughter of a Riker Vice-President asked: "Why can't you make my asthma medicine like mother's hair spray" and this was the stimulus for the pMDI [22]. It is readily apparent that finding solutions to problems or meeting needs are clear drivers for the invention of alternative technologies. However, the nature of the inventions depends *inter alia* on serendipity, chance comment, or the experience of the inventor. The experience can be recent or old, scientific or non-scientific. For example, the need to deliver doses of sodium cromoglycate, which exceed the capacity of pMDI, was the stimulus. The technology (Spinhaler - patented 1963) with its rotating vibrating propeller, was invented by a former Spitfire pilot [6].

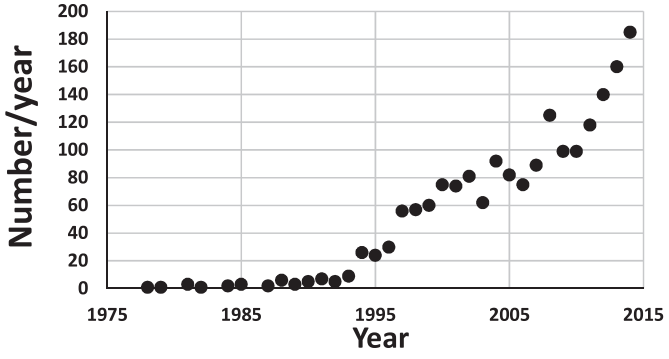

Fig. 2. Number of published research articles per year on 'dry powder inhal*'.

6. Regulation

The nineteenth century was a century of charlatanism and quackery in addition to care by well-meaning physicians. The English physician John Mudge for example, described his invention of an inhaler based on a pewter tankard, in his 1778 book 'A Radical and Expeditious Cure for a Recent Catarrhous Cough'. Dr Mudge is thought to be the first person to use the term "inhaler," and describes using his device for inhaling opium vapour for the treatment of cough [23]. Direct-to-consumer advertising by way of pamphlets, booklets and newspaper advertisements informed the public about inhalation therapies and devices for the treatment of consumption, catarrh, croup, bronchitis, pertussis, diphtheria, or influenza [23]. In 1906 the FDA imposed restrictions on advertising leading to the demise of quack cures and so that the innovative physician was gradually replaced by the scientist and then the research team. Even regulation aimed at environmental issues has influenced the direction of aerosol R&D.

The United Nations' Montreal Protocol (1987) which banned substances that deplete the ozone layer required the phasing out of CFC in air-conditioners etc by 1996. Although pharmaceutical companies had exemptions and the environmental impact of CFC in therapeutic aerosols was negligible, they chose to find alternative

propellants (hydrofluoroalkanes). But it was also a stimulus for the development of dry powder inhalers [24]. However, much of the effort to engineer particles to achieve efficient aerosolisation used approaches and technologies from oral drug delivery. Approaches such as spray drying [25], traditional matrix or coated systems [26] from oral drug delivery science were tried. These approaches were empirical, solution oriented, and not ideal for developing scientific understanding of the mechanisms operative in aerosolisation of powders. Systems were inefficient with low fine particle fractions and variable emitted doses. More emphasis needed to be placed on engineering particles with optimal properties [27]. Research on the mechanisms of powder aerosolisation, necessary for rational engineering of particles, developed more slowly over the following decades.

Regulation has also driven the effort and resource put into the approval of new aerosol systems. Once the time period from idea (new drug, new formulation, new device) to the patient was short. Now regulation requires that the new product meets quality, efficacy and safety criteria through expensive clinical trials. As at Feb 2014, based on a search for 'Inhaler' on https://clinicaltrials.gov/, there were 27 ongoing clinical trials [28] and in June 2015 there were 124 ongoing trials and a further 775 closed trials listed. Regulation has driven not just the translational aspects of aerosol delivery, but also the need for evermore detailed understanding of all aspects of the science of DPIs.

7. Instruments and assays

Access to meaningful data is a major determinant of the direction of a scientific field. In this regard it is often major equipment which springs to mind (electron microscopy, gamma scintigraphy, laser diffraction particle sizers, etc). Simple inventions (electronic balance, Eppendorf pipettes), analytical kits, availability of radiotracers, cell culture techniques, etc have also played their role in accelerating research [29]. Nevertheless, it is arguably the more sophisticated equipment which has enabled the major advances and even changes in direction of the field.

In the 1960s, pharmaceutical science was able to shift its focus from in vitro issues (e.g. stability) to in vivo challenges, because of the availability of GLC and HPLC equipment. This 'kit' simplified the quantification of drug in biological matrices, particularly plasma. Although blood levels had been quantified by radiotracer and radioimmunoassay methods, GLC and then HPLC simplified the process enormously. This new ability was the *raison detre* for pharmacokinetics, a new field in the pharmaceutical sciences, and it developed rapidly in the subsequent decades [30]. So here is an example where the shift in research focus from bottle to body was enabled by the availability of new equipment, which of course had been enabled by research and development on separation science, materials science, electronics and engineering.

By the 1860s, the efficacy of some inhalations was no longer doubted. Indeed, inhalants were included in the British Pharmacopoeia for the first time in 1867. Nevertheless, there were questions about how deeply inhaled therapies penetrated the lung structures. It was suggested that there could be changes in the inhaled materials depending on temperature and that the device would influence the penetration. What dose to use was also a question of interest. In what might have been one of the first deposition experiments, a woman with a tracheal fistula was given an inhalation. Subsequent chemical tests at the tracheal opening showed that the inhaled substances had at least penetrated as far as the trachea [31] – hard won data indeed. Mostly, physiological and therapeutic experiments were the only reasonable methods which suggested the aerosol was penetrating [32]. But what fraction of the dose and how deeply did the aerosol penetrate were unknown.

The drive to understand the disposition of aerosols in the lung came from concerns about toxicity of powder aerosols in the workplace – industrial hygiene. Inhale-exhale experiments were conducted using defined aerosols with analysis of the difference in the analyte concentration in inspired and expired air [33,34]. Although this method provided some understanding of the dose in the lung, it provided no information about the distribution of the particles in the respiratory system. Consequently, theoretical models were developed (at least as early as 1935 [23]) using the improving morphometric descriptions of the pulmonary system to attempt to predict distribution of particles of various sizes in the lung [35–38]. Studying deposition patterns has become possible with the availability of modern radionuclide imaging methods. The early gamma-ray camera [39] was primitive by today's standards but it enabled far improved understanding of aerosol deposition in the lungs and how this is influenced by breathing patterns, patient coordination etc. New three dimensional methods (SPECT single photon emission computed tomography; and PET, positron emission tomography) give superior regional lung deposition data [40].

Convenient instrumental methods enabled by ever increasing computing power facilitated understanding of deposition of particles in the respiratory system and, importantly, how the deposition pattern is influenced by the characteristics of the particles. The physical characteristics of a powder that are determined first and foremost are particle size and size distribution. Laborious microscopic techniques were partially displaced in the 1970s when the laser diffraction method of particle size analysis became available. However, because of the limited computing power (PCs were limited to 8K of RAM) the Fraunhofer approximation was used rather than the more accurate Mie theory. The approximate method could misinterpret diffraction data suggesting that bimodal distributions existed when they didn't, as well as overestimating particle size. These errors are significant in the particle size region of interest for PDIs [41]. Since about 2000, Mie theory has been used because of the computing power available for these more complex calculation.

Given understanding of particle distribution in the lung, some pharmaceutical scientists recognized the need for improved characterisation and understanding of particles and their interactions and how these factors influence aerosolisation. They were driven by the belief (gestalt) that through mechanistic understandings comes predictive power which can be used to design effective DPIs. Research on particles and their interactions has been enabled by an ever increasing number of powerful instruments (Table 2).

8. Mechanisms of aerosolisation of powders – knowledge transfer and debate

The early research (1980s) that sought to understand aerosolisation of powders for inhalation is an example of knowledge transfer. It was based on earlier research on interactive powder mixes for oral delivery done in the 1960–70s [62–66]. The fact that the theory was eventually transferred is rational; the fact that much research on DPIs was done without invoking the earlier theory was less-than-rational. Initially, the theory presumed perfect interactive mixes in which the fine drug particles were dispersed on larger carrier particles. Aerosolisation was perceived as a detachment process so it was important to understand adhesional forces between particles [67] and what factors might influence them, e.g. humidity [68–70]. As various characteristics of the drug and carrier particles were studied (Table 3) it became clear that DPIs are not perfect interactive systems.

Researchers sought to understand how the adhesional forces could be engineered. Could the surface energy of particles be lowered, by eliminating high energy amorphous sites, if particles

Table 2
Some of the instruments used to characterise particles, particle interactions and aerosolisation. This table is not meant to be comprehensive but to note some early applications of equipment in DPI research.

In vitro characterization of aerosolisation			
1969	Cascade Impactor	First use of cascade impactor for pharmaceutical aerosols	[42]
1971	Andersen Cascade Impactor (ACI)	An updated 8-stage impactor was used in Riker Laboratories for aerosol characterisation	[43]
1973	Multi-Stage Liquid Impinger (MSLI)	The pharmaceutical applications of MSLI described	[44]
1986	Twin impingers	Two single impaction stage instruments (steel made and glass made) named 'twin impingers' included in British Pharmacopoeia	[45–47]
2000	Next Generation Impactor (NGI)	The NGI launched.	[43,48]
Microscopic characterization of particles			
1965	Scanning Electron Microscope (SEM)	Cambridge Instrument Company markets SEM	[49]
1988	SEM	Disodium cromoglycate DPI labelled with ^{99m}Tc characterized by SEM, cascade impactor and in vivo by gamma scintigraphy	[25]
1998	Hot stage microscopy	Crystallisation of amorphous lactose in spray dried rhDNase-lactose DPI characterised by hot-stage microscopy – and other techniques (SEM, DSC, TG, FTIR, X-ray powder diffraction)	[50]
1999	Transmission electron microscopy (TEM)	TEM (and other techniques: SEM, freeze fracture SEM, X-ray powder diffraction) used to characterise spray-dried mannitol	[51]
2001	Confocal laser scanning microscopy (CLSM)	Spray dried nonporous corrugated BSA particles characterised by CLSM – and other techniques (SEM, surface area analyser, XRD, TGA)	[52]
2006	Energy-dispersive X-ray (EDX) - SEM	Drug/drug and drug/excipient spray dried mixes characterised by EDX - and other techniques (XRD, SEM, DSC, impinger)	[53]
Measuring interactions between particles			
1986	Atomic Force Microscopy (AFM)	AFM invented by Binnig in 1986 commercialised in 1989	
2001	AFM–Scanning probe microscopy (SPM)	Scanning probe microscopy (SPM) used to measure directly the adhesion of individual lactose particles to the surface of gelatin capsules employed in DPI, and shortly after to measure interactions in ternary mixes of dry powders.	[54,55]
Characterization by spectroscopic methods			
2004	X-ray photoelectron spectroscopy (XPS)	XPS instrument commercialised in 1969. Surface of spray dried particles of albumin, DPPC and a protein stabilizer analysed by XPS shows surface enrichment with DPPC.	[56]
2006	Time-of-flight secondary ion mass spectroscopy (ToF-SIMS)	SIMS experiments done in the 1940 and used in material science in 1960s. 2006: Blister packaging material used in DPIs characterised by ToF-SIMS	[57]
2008	Raman	Raman spectroscopy used to measure content uniformity of two intermediate products of a DPI	[58]
Measuring the surface energy of particles			
1970s	Inverse Gas Chromatography (IGC)	1941: IGC used to measure partition co-efficient between two liquids; 1970s: used to study the surface and bulk characteristics of polymers and their mixtures	[59]
1994	IGC	IGC used to characterise the surface properties of salbutamol sulphate for inhalers in 1994; and of lactose used in DPI in 1996	[60,61]

were produced by a supercritical fluid technique [71]. Others produced 'smoothed' particles of lactose using a patented method, with and without the addition of magnesium stearate, and measured the surface roughness by tapping-mode AFM and interparticle adhesion forces using AFM [72]. They showed that the 'smoothed' powder had a lower specific surface area (BET adsorption method) and noted that this could be due to decreased rugosity of the particles but also due to a reduction in the percentage of fines in the powder. However, AFM confirmed that the rugosity was indeed reduced, that the detachment force was also reduced, and that this translated into improved aerosolisation as measured by two-stage impinger. Conversely, others showed improved aerosolisation with spray-dried 'corrugated' particles, and perhaps this was because the contact area between particles was reduced due to their roughness [52].

In such seemingly simple yet complex systems, apparently contradictory findings can occur, and this can result in important scientific debate. DPIs are difficult to characterise even with sophisticated equipment. Different results may arise from: sample preparation techniques, batch-to-batch differences in drug and excipient, storage effects (temperature, relative humidity, time of storage) etc. Even when results are not contradictory, creative scientific minds may develop alternative mechanistic hypotheses to explain the data and this can lead to interesting debates in the literature and at conferences. It would be naïve to think that such debates are always rational. Scientists are human so that rationalism can sometimes be mixed with ego, bias, 'pet theories', etc - and yet science advances. Sometimes, both protagonists in an argument will be partially right and partially wrong. And finally, the agreed hypothesis may be shown subsequently to be incomplete. An example of healthy debate in the DPI literature relates to the addition of fine excipient particles (e.g., fine lactose) to a binary mix of drug and large carrier particles. This has been shown to improve aerosolisation, but the mechanism was debated and is still uncertain.

Two hypotheses have been suggested: the fine lactose passivates the large carrier surface, leaving only weak attractive sites (active site theory) [73]; the fine carrier affects agglomeration

Table 3
Factors which have been studied to understand the aerosolisation of DPIs.

Drug	Carrier	Binary mixes	Ternary mixes
Particle size	Size	Drug concentration	Fine concentration
Particle shape	Shape	Drug-carrier ratio	Fine lactose
Crystallinity	Crystallinity	Mixing time	Other fine sugars
Hydrophilicity	Surface roughness	Mixing speed	Drug-fine ratio
Hydrophobicity	Different sugars	Influence of relative humidity	Size of fine
	Hydrophobicity	Drug-carrier adhesion	Shape of fine
			Drug, fine and carrier mixing processes

(mixed agglomerate theory) of the powder and that deagglomeration of the powder is an important step in the aerosolisation process [55]. Indeed, both theories may be correct and both theories are predicated on interaction of fine lactose with other particles. Subsequent work showed the size of the fine lactose to be important in the agglomerate structure and aerosolisation [74]. Resolution of such debates, in part, depends on an even more fundamental understanding of particle interaction and agglomerate strength.

Adhesion/cohesion forces were studied in the field of mineralogy before the pharmaceutical sciences and in this IGC has played an important role [75]. IGC has now been used to probe the surfaces of pharmaceutical particles to tease apart nonpolar and polar components of surface energy [76,77]. With such information, and supported by fundamental theories (JKR theory [78] and DMT theory [79]) interparticle interactions can be predicted with more confidence.

While adhesion-cohesion forces directly influence the detachment of one particle from another, de-agglomeration of particle masses to particles of primary size is more complex. Research on the agglomerate strength of solid dosage forms, such as tablets, commenced in 1960s, long before the interest in powders for inhalation [80]. In the context of oral solid delivery, a simplified model was proposed to describe tensile strength of a powder [81] and recently this theory was used to provide a mechanistic understanding of the deagglomeration of powders during aerosolisation [74,82]. The approach assumes a homogeneous powder bed, whereas it is actually heterogeneous. Hence improved mechanistic understanding and prediction requires a theoretical model which accounts for the distribution in powder strength [83,84].

9. Conclusions

Research on DPIs has two broad aims: mechanistic understanding of relevant physical-chemical-biological processes which influence DPI efficacy; improved care of people with respiratory diseases. This article has given more emphasis to the formulation aspects of DPI, and only touched on devices. But there is an equally interesting detailed story to be told about research and development on devices, which is heavily dependent on chemistry, materials/polymer science, device-engineering, anatomy/physiology and behaviours of patients. Based on information in the public domain, it is concluded that the research has taken a meandering course, sometimes rational, sometimes less-than-rational. It has been influenced by historical and cultural beliefs, luck, chance comment, communication, debate, and regulation. The availability of equipment to characterize particles and powders, and to study their in vivo disposition, has had a major influence of the direction of the research. The discipline has borrowed from or been influenced by science from closely related (e.g. oral drug delivery) or distantly related (mineralogy, industrial hygiene) disciplines, but sometimes the time period for this knowledge transfer has been surprisingly long. Other scientific disciplines are probably no different.

Conflict of interest

None.

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