Journal of Drug Delivery Science and Technology 30 (2015) 310–317

Contents lists available at ScienceDirect

Journal of Drug Delivery Science and Technology

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

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

I.G. Tucker [a, *], S.C. Das [a], P.J. Stewart [b]

[a] New Zealand's National School of Pharmacy, University of Otago, P.O. Box 56, Dunedin 9054, New Zealand
[b] Drug Delivery, Disposition and Dynamics, Monash Institute of Pharmaceutical Sciences, Monash University, 381 Royal Parade, Parkville, Victoria 3052, Australia

ARTICLE INFO

Article history:
Received 17 May 2015
Received in revised form
10 June 2015
Accepted 10 June 2015
Available online 12 June 2015

Keywords:
Drug delivery
Dry powder inhaler
Inhalation

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

* Corresponding author.
E-mail address: ian.tucker@otago.ac.nz (I.G. Tucker).

http://dx.doi.org/10.1016/j.jddst.2015.06.008
1773-2247/

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 deagglomeration 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