



Review

Phytoconstituent based dry powder inhalers as biomedicine for the management of pulmonary diseases

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ABSTRACT

Pulmonary disease represents a major global health issue. They are commonly treated by various synthetic molecules. But, frequent high-dose of oral and injectable drugs may lead to severe side effects and this juncture demands inhaled formulations that facilitate effective drug delivery to the lower airways with negligible side effects. Natural phytoconstituents or phytoalexin (i.e. plant antibiotics) have showed a unique treatment array with minimum side effects and great capability to treat intrapulmonary and extrapulmonary diseases compared to synthetic drugs. Moreover, the progress of disciplines such as nanotechnology, material science and particle engineering allows further improvement of the treatment capability and efficiency. This article review and analyze literatures on inhaled phytoconstituents which were published in the last 10 years. Additionally, it will also offer the researcher with some basic background information for phytoconstituents profile, formulation requirements and drug delivery systems.

1. Introduction

Lung diseases are one of the leading causes of death globally, characterized by airflow limitation, loss of elasticity, chronic inflammation, emphysema, bronchoconstriction and mucus hyper secretion. Several factors including genetics, tobacco smoke, air pollution, inhalation of noxious particles, occupational chemicals and dusts have shown to contribute to the development of lung disease. Some of the most widespread are asthma, chronic obstructive pulmonary disease (COPD), occupational lung diseases and pulmonary hypertension [1]. In World, more than 500 millions peoples are suffering from various lung diseases [2]. In present drug discovery era, a variety of chemically synthesized molecules are approved by regulatory bodies and are coming on the marketplace, having good therapeutic value but this therapy causes serious side effects which could be life threatening. Conventional therapy provides non-targetability in body due to peak and valley fluctuations of plasma drug concentration and a frequent dose of administration can produce troublesome for allopathic therapy lead to poor patient compliance. Thus, main stream allopathic medicines has begun to relocate on herbal medicines as a primary means to deal with crucial health problems, also said as ‘Back to Mother Nature’. Approximately 80% of the present world population relies on use of

herbal medicines for their primary health care and other needs which denotes the scope of herbal medicines. Furthermore, herbal medicines own variety of therapeutic actions and are less-toxic with fewer adverse effects. According to the World Health Organization (WHO), the use of herbal medicines all over the globe exceeds conventional drugs by a factor two to three times [3]. Presently, herbal medicines have regained their reputation for treatment of lung diseases with their efficiency and safety feature being strongly supported by controlled clinical trials [4]. Current global research has also presents valuable inputs about specific mechanism of action of these herbal alternatives [4,5]. Thus, in this review, an effort has been made to touch upon various aspects related to development of herbal medicines including their impact on lung disease and other essential physicochemical features of drug delivery systems are also discussed in detail.

2. Methodology

An extensive bibliographic research was performed to provide a carefully insight into the use of herbal medicines (phytoconstituents) for pulmonary diseases. We performed a literature search using various scientific engine and databases such as Google Scholar, Science Direct, PubMed, Scopus and SciFinder. This article reviews different aspects

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related to phytoconstituents pulmonary delivery with special emphasis on the manufacturing techniques, in-vitro and in-vivo aerosol performance. References listed in present review include 66 articles, containing 34 original research articles, 27 peer reviewed articles, 1 WHO fact sheet and 4 books. Whereas unpublished dissertations and conferences communications were excluded. All searches ended at June 2018. Two authors (Mehta and Bothiraja) carried out an extensive literature search independently. All articles were screened carefully according to title and then chosen after abstracts were comprehended. All chemical structures have been revised using open chemistry database PubChem and then drawn using ChemDraw software (Version 12.2; Perkin Elmer).

3. Phytoconstituents

Herbal medicines have made indisputable contributions from ancient civilizations and created one of the basics for healthcare in almost all cultures across the globe [6]. The use of herbal medicines is an essential part of any traditional medicine system which is performed in several manners in various cultures of the humanity [7,8]. Regardless of their extensive practice as medicinal products, communities interest in herbal medicines is even rising with special emphasis on their pharmaceutical, clinical and economic significance. Herbal medicines themselves are well recognized for their huge diversity of biological functionality and variety of chemical structures. This makes herbal medicines more appealing as key elements for new drug development. They are become of more interest due to their significance in modern medicines such as pharmaceutical intermediates, chemical entities for synthetic drugs, food supplements and nutraceuticals [7,9].

Since the beginning of this century, the growth of powerful analytical tools and technologies, such as materials science, bioinformatics, computer-aided screening and cell biology have acquired rapid growth in field of clinical and analytical characterization. These tools and technologies offer new opportunities to categorize and characterize a sole chemical moieties. Thus, in spite of usefulness, traditional herbal preparations have been left over and cannot be believed as a end points. In its place, specific phytoconstituents are isolated and characterized to synthesized respective drug analogues. These, phytoconstituents are nothing but the chemical moieties that appears naturally in plants and which are responsible for various organoleptic and therapeutic features of plants [10]. More specifically, this chemical moieties are secondary metabolites such as alkaloids, glycosides, polyphenolic compounds and etc. Phytoconstituents and their health related consequences have been extensively scrutinized in this century. Their therapeutic outcomes are of main interest because of their role in prevention of major life threatening diseases such as cancer, cardiovascular complications and respiratory infections. These diseases are leading causes of death nowadays which signifies that phytoconstituents will persist to be matter of scientific community interest. Based on practical health benefits such as anti-oxidant, anti-inflammatory and immuno-modulatory, phytoconstituents may act as a budding additive and/or an alternative therapy [7,9].

4. Phytoconstituents in inhalation delivery

It is an appealing to think of inhalation therapy as a novel approach for drug delivery, but this therapy has been well documented in most of the ancient cultures and it has a strong history of more than 4000 years [11]. With the growth of disciplines, such as medical science, material engineering and molecular pharmacology have acquired a massive growth in field of inhalation therapy. At the same time, we have now raised our visions higher, trying to utilize this non-invasive therapy to treat various extrapulmonary diseases also [12].

Lung, is persistently exposed to an environment rich in oxygen and thus prone to injury caused by oxidative stress (Fig. 1). So as to impede lung tissue damage, lung is endowed with various antioxidant

protections such as glutathione, superoxide dismutase, β -carotene, vitamins C and E, uric acid and heme-oxygenase [13–15]. However some time reactive oxygen or nitrogen species defeat biological antioxidant protections and an oxidative stress leads to a number of lung disorders. Recently, several scientific reports have verified the assumption of oxidative injury in cystic fibrosis, asthma, COPD and a direct injury to epithelial cells by reactive oxygen species [13,15]. Existing therapy is used to control abnormal mucus secretion and inflammation in order to delay lung tissue damage. Only a few treatment options are available for lung tissue damage, such as oral/inhaled corticosteroids or high doses of oral *N*-acetylcysteine. But, these treatments have limited beneficial actions in presence of considerable adverse effects [14]. Therefore, enrichment of biological antioxidant protections through a pharmacological treatment or a diet might be a suitable approach in treatment of pulmonary disease. Among the natural antioxidants, cautious consideration has been focused on phytoconstituents such as flavonoids i.e. polyphenolic compounds. Antioxidant, anti-inflammatory and antibacterial activities of polyphenolic compounds are well-documented. Despite the health benefits, low bioavailability of phytoconstituents has become a problem of concern for formulation scientist. Phytoconstituents exhibit a low bioavailability because of their poor aqueous solubility, poor membrane permeability, high molecular weight, degradation in gastric pH, inclination to oxidation and very low dissolution rate, heading to an irregular absorption from oral solid dosage forms [16]. Even though a number of scientific reports have been focused on antioxidant and anti-inflammatory effect of polyphenolic compounds, only few scientific publications has been addressed to their formulation in order to enhance the bioavailability [14]. More recently, orally delivered various nanocarriers and microparticles have been designed and tested. Furthermore, various lipid vesicles such as are also liposomes, spherulites and cochleates are also widely explored for drug delivery of phytoconstituents. Still, oral administration of these systems leads to poor therapeutic response because of first pass metabolism and enzymatic degradation within gastrointestinal tract (GI) [17]. To tackle these issues and to make phytoconstituents therapy more effective there is a strong need of an alternative therapy. An alternative approach might be to attain superior local concentration of antioxidant and anti-inflammatory compound in lung tissue by distributing aerosol directly to airways by a nebulizer, a pressurised metered dose inhaler (pMDI), soft mist inhaler (SMI) or a dry powder inhaler (DPI) [13]. Compared to other inhalation techniques, DPIs are more handy, they are propellant-free, didn't require reconstitution of powders or cold chain storage, no need for coordination between patient inspiration and inhaler actuation, more opportunities for carrier engineering and are less expensive [11,18]. Lastly, DPIs can enhance phytoconstituent physicochemical and biopharmaceutical properties and can guarantee a delivery of higher drug concentration at the deposition site (Fig. 2).

5. Phytoconstituents based dry powder inhalers

Pulmonary drug delivery system of phytoconstituent is an unique delivery strategy and has become of a greater interest in field of drug delivery research due to its simple manufacturing process, capability of treating various intrapulmonary and extrapulmonary diseases, improved therapeutic effects with minimum adverse events. Simply, these delivery systems can provide safe, reliable and easily accessible improved treatment options. Thus, present section reviews and analyze literatures on inhalable phytoconstituent agents which were available in the past 10 years. Various novel drug delivery systems for inhaled phytoconstituent with their key findings are described in Table 1.

5.1. Polyphenols

5.1.1. Curcumin

Curcumin (CUR) is a natural yellow-orange color hydrophobic

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