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UNDERSTANDING THE EVIDENCES AVAILABLE FOR USE OF TRANSDERMAL PATCHES IN THE TREATMENT OF ASTHMA – A REVIEW

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ABSTRACT: Transdermal drug delivery systems (TDDS) offers a route that by-passes the gut and hence they are more convenient. They are also non-invasive and safer than the other alternatives. The transdermal or the adhesive patches are used to deliver a specific quantity of drug in a controlled release manner through skin for over a long period of time. There are many types of patches like the matrix, membrane, reservoir, micro reservoir etc. These patches have been in use to deliver many classes of drugs like analgesics, anti-pyretics, anti-diuretics, anti-asthmatics, etc. There are many anti-asthmatic products that are available in the form of transdermal patches internationally like the tulobuterol, salbutamol, ketotifen, etc., but the question is about their usage and availability. The primary aim of this review is to understand the availability of evidences for and against the use of TDDS for asthma. Most studies, both *in vivo* and *in vitro*, and both as add-on and as a monotherapy have yielded positive results.

INTRODUCTION: In recent times, respiratory diseases like asthma and chronic obstructive pulmonary diseases (COPD) were ranked as the top killer diseases in urban and rural areas. In spite of the advances in understanding of the disease and availability of improved medications and information on treatment, the morbidity and mortality of these two diseases are increasing.[1] Asthma is a complex disease of varied etiology triggered by numerous factors such as allergens, chemicals, exercise, drug, cold dry air, infections and emotional fluctuations.

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Despite major advances in understanding the etiology and pathophysiology of asthma and the development of new therapeutic modalities, the prevalence, severity, and mortality from asthma have increased five times in children over the past 20 years. Mortality seems to be particularly high in minority populations in the urban as well as the rural areas. [2] As on 2009, 300 million people worldwide are affected by asthma leading to approximately 250,000 deaths per year.[3]

It is estimated that asthma has a 7-10% prevalence worldwide.[4] As of 1998, there was a great disparity in the prevalence of asthma across the world, with a trend toward more developed and westernized countries having higher rates of asthma [5] with as high as a 20 to 60-fold difference. Westernization, however, does not explain the entire difference in

asthma prevalence between countries, and the disparities may also be affected by differences in genetic, social and environmental risk factors.[6] Mortality, however, is most common in low-to-middle income countries, while symptoms were most prevalent (as much as 20%) in the United Kingdom, Australia, New Zealand, and Republic of Ireland; they were lowest (as low as 2-3%) in Eastern Europe, Indonesia, Greece, Uzbekistan, India, and Ethiopia. [7]

India has approximately 15-20 million asthmatics and 10 to 15% of Indian children between the ages of 5 and 11 years have symptoms of asthma.[8] There is a median prevalence of about 2.4% in adults of over 15 years of age in the Indian population. Prevention and long-term control are key in stopping asthma attacks before they happen. Treatment usually involves learning to recognize the triggers, taking steps to avoid them and tracking breathing to make sure that the daily asthma medications are keeping symptoms under control. In case of an asthma flare-up, there may be a need to use a quick-relief inhaler, such as albuterol. The main goal in treatment of asthma is more effective control of the disease, which ensures that the asthmatic patients are able to lead a normal, physically and emotionally active life. A comprehensive pharmacotherapeutic management is required to solve the above objectives. This includes the following:

1. Early diagnosis of asthma and assessment of severity;

2. Control to exclude smoking habit and less exposure to triggers such as viral infections and allergens; limited use of medications so that it reduces side effects and cost of drug by using the most appropriate delivery system;

3. Patient's follow-up and regular re-evaluation (both clinical evaluation and quality of life).

Best management of asthma includes avoidance of triggers, more environmental control, pharmacotherapy, and patient education.[9]

The current pharmacotherapeutic management includes medication classification like inhaled corticosteroids, leukotriene modifiers, long-acting beta agonists, theophylline, combination inhalers, short-acting beta agonists, quick-relief (rescue) medications, ipratropium, immune modulators, etc.[10]

In theory, avoidance of triggers may prevent asthmatic symptoms and improve quality of life, however, persuading asthmatic patients to stop smoking or to avoid favorite animals that trigger wheezing episodes etc., may not be so easy practically. Much evidence has emerged showing the benefit of self-management plans and the work by de Vries *et al.* seeks to answer the important question of the added value of mattress covers in patients already on management plans. They showed that the semi-permeable covers led to a significant reduction of the allergen levels in the mattress, but sadly this was not shown to translate into a significant reduction in the dose of inhaled steroids needed to control asthma. Overall measures to avoid house dust mite have not been shown to make dramatic differences to the average patient with asthma (although, of course, there may be some who defy the average and respond dramatically).[11]

One of the current difficulties with the evidence base for asthma management is that most research has been carried out in the adult population. For this reason, licensing of medication is more restricted in children and the consequence is a substantial quantity of 'off-label' prescriptions, as shown by Mc Cowan et al.[12] The particular issue of the lack of data with respect to paediatric asthma and the use of long-acting β_2-agonists was highlighted by Bisgaard in the Lancet, who argues strongly that the treatment for children with asthma needs to be based on trial data in children (rather than extrapolation from results in adults), and suggests that the licensing authorities should demand more studies in children. He also points out that the BNF for Children stresses the importance of discontinuing long-acting β_2-agonists in children if there is no response.[13]

Dangers could arise if patients with asthma find that their usual symptoms of deterioration are masked by inhaled β_2-agonists, and they consequently delay obtaining a rescue course of

oral steroids for an exacerbation. Doubling inhaled corticosteroids has produced disappointing results in trials, so it is important to ensure that patients on long-acting β_2-agonists understand that serious asthma attacks should not be ignored, and early use of a short course of oral steroids remains the most likely way to avoid deterioration leading to a hospital admission.[14, 15]

The novel technologies in pulmonary drug delivery propelled the development of new strategies for pharmacological intervention in human diseases. In particular, this review will focus on pulmonary parameters which influence the delivery of inhaled therapeutics and summarize novel applications and recent innovations. The central issues of pulmonary drug application are optimal effectiveness under conditions of greatest safety. They not only depend on the properties of the drug, but also feature the application vehicle and drug formulation. The optimization of the whole system (drug, formulation, and vehicle) is therefore a necessary prerequisite for inhaling medicines.

Depending on the desired area of action of drug, the inhaled medicine has to be adjusted to particle size, chemical composition and concentration to guarantee a local or systemic drug action. Local asthma therapy represents the established concept for inhalation therapy. Due to the disease status, deposition of drugs is therefore often seen in central rather than peripheral airways. Recent developments in ultrafine therapeutic particles should therefore provide enough drug deposition even in the deeper interior airways. There are increasing number of Pulmonary drug delivery novel innovations in pipeline and some have come out successfully in the near past. Successful feasibility of these novel concepts in pipeline can be expected in the near future.

Transdermal drug delivery systems offers a route that bye-passes the gut and are more thoroughly convenient. They are non-invasive and safer than the other alternatives. TDDS is better suited for long-term drugs. The transdermal or the adhesive patches are used to deliver a specific quantity of drug in a controlled release manner through skin for over a longer period of time. There are many types of patches like the matrix patch, membrane patch, reservoir patch, micro-reservoir patch, etc.[16] The transdermal patches have been in use to exert many activities like analgesic, anti-pyretic, anti-diuretic & anti-asthmatics, etc. in the past and the present. There are many anti-asthmatic products that are available in the form of transdermal patches internationally like tulobuterol, salbutamol, and ketotifen. But, the question is about their usage and availability. To understand the evidences for the use of patches, we aim to review various anti-asthmatic products available in the form of transdermal patches. Hence, the primary aim of this review is to understand the availability of evidences for and against the use of TDDS for asthma.

Methodology:

A systematic search strategy was devised to identify the anti-asthmatic drugs available as transdermal patches. Relevant medical websites and databases were searched. To qualify for inclusion, the study should have used or developed transdermal patches and evaluated its efficacy in either humans or animals. The following criteria were also considered for inclusion of a study in this review: the articles should be published in English and it should be published in a peer-reviewed journal.

We searched databases like EMBASE and Scopus from Elsevier, Medline from PubMed, and Google Scholar using keywords like asthma, transdermal, patches, controlled drug delivery, transdermal delivery, antiasthma, and antiasthmatic.

In addition, experts in the field were contacted to select studies that meet the criteria, and we also looked up references of key articles. The authors read the articles in full and extracted the data in a standardized fashion. Hence, this review presents 18 studies using antiasthmatic drugs in a transdermal patch form in humans as well as in animals to evaluate its efficacy in controlling asthma. We have not reviewed the original data behind the studies listed here. We have, in all cases, took original author's representations as true and evidence-based.

RESULTS:

S. No	Title	Drug	Year	Type of Study	Sample Size
1	Addition of transdermal or inhaled long-acting Beta2-agonists in adult asthmatic patients treated with inhaled corticosteroids: switchover study from tulobuterol patch to salmeterol dry powder inhaler [17]	Tulobuterol & Salmeterol	2015	*In vivo*	64
2	Iontophoretic and Microneedle Mediated Transdermal Delivery of Glycopyrrolate [18]	Glycopyrrolate	2014	*In vitro*	_
3	Transdermal application of steroids to cervical trachea for the cough in patients with bronchial asthma and cough variant asthma –A pilot study [19]	Corticosteroids	2013	*In vivo*	28
4	Effects of transdermal tulobuterol in pediatric asthma patients on long-term leukotriene receptor antagonist therapy: results of a randomized, open-label, multicenter clinical trial in Japanese children aged 4-12 years [20]	Tulobuterol & LTRAs	2013	*In vivo*	62
5	Effects of Tulobuterol patch on the treatment of acute Asthma exacerbations in young children [21]	Tulobuterol	2012	*In vivo*	86
6	New percutaneous absorption herbal patch for Asthma of paracmasis and its effect on the relative transcription factors of patients [22]	Herbal patch	2012	*In vivo*	120
7	Transdermal patches for ketotifen fumarate (KTF) as asthmatic drug [23]	Ketotifen fumarate	2009	*In vitro*	_
8	Ketotifen fumarate and salbutamol sulphate combined transdermal patch formulations: *In vitro* release and Ex vivo permeation studies [24]	Ketotifen fumarate & Salbutamol sulfate	2013	*In vitro*	-
9	Tulobuterol patch maintain diaphragm muscle contractility for over twenty –four hours in a mouse model of sepsis [25]	Tulobuterol	2009	*In vivo*	50
10	Effects of the addition of beta-2 agonist tulobuterol patches to inhaled corticosteroid in patients with asthma [26]	Tulobuterol	2009	*In vivo*	65
11	Transdermal treatment with tulobuterol increases isomeric contractile properties of diaphragm muscle in mice [27]	Tulobuterol	2007	*In vitro* and *in vivo*	70
12	Preparation and evaluation of transdermal patches of terbutaline sulphate [28]	Terbutaline sulphate	2006	*In vitro*	_
13	Comparison of the effect of tulobuterol patch and salmeterol in moderate to severe asthma [29]	Tulobuterol and salmeterol	2006	*In vivo*	54
14	Formulation and evaluation of controlled release transdermal patches of theophylline –salbutamol sulphate [30]	Theophylline and salbutamol	2006	*In vitro*	_

15	Clinical pharmacokinetic and pharmacodynamic evaluation of transdermal drug delivery systems of salbutamol sulphate [31]	Salbutamol sulfate	2004	*In vitro*	_
16	Clinical evaluation of tulobuterol patch in patients with mild or moderate persistant bronchial asthma - Effects of longterm treatment on airway inflammation and hypersensitivity [32]	Tulobuterol	2004	*In vivo*	36
17	Effects of sustained release tulobuterol on asthma control and beta adreno receptor function[33]	Tulobuterol	2002	*In vitro*	_
18	Development of Transdermal Formulation of Tulobuterol for the Treatment of Bronchial Asthma [34]	Tulobuterol	2002	*In vitro* and *in vivo*	_

DISCUSSION: All studies identified for review which qualified the inclusion criteria were from the 21st century only starting from 2002 and majority were from Japan which may probably be the pioneering transdermal anti asthmatic country. Out of the total of 18 studies 9 were In vivo studies and 7 were in vitro studies and 2 were both in vivo and in vitro studies. 10 studies out of the 18 involved Tulobuterol and its combinations as transdermal preparations. One study conducted in 2012 was done using some herbal formulation in patch form. One study each involved salbutamol, glycopyrollate, corticosteroids, Terbutaline, Theophylline and two studies involved Ketotifen. So the largest studied molecule was Tulobuterol and in recent times the no and volume of study has been increasing. We did not analyze the type of the study or we did not get into the details of the design. The aim was to find out the number of studies in the area of interest, i.e., studies involving Transdermal patches for treatment or control of Asthma.

CONCLUSION: The above studies describe the usage of transdermal patches in the treatment as well as in the control of asthma. Almost all studies have shown positive results for most of the transdermal patches – both *in vivo* and *in vitro*. There are studies that have observed the effects of patches as monotherapy and in combination also with other anti-asthmatic medications.

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