A Review on Novel Approaches to the Treatment of Asthma

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Abstract: *Asthma is among the most prevalent disorders of the respiratory system, affecting more than 300 million people worldwide. It is a heterogeneous and intricate inflammatory disease of the airways with complicated underlying events yet to be unleashed. Despite of advances in the introduction of newer therapies, the symptoms and exacerbations caused by asthma continue to prevail. Hence, there is an emerging need for new drug delivery mechanisms to achieve therapy unrestricted to symptomatic relief as well as to overcome the hindrances faced by conventional drug delivery systems. The present review highlights a brief overview of the disease and the rising superiority of novel drug delivery systems over conventional systems in its treatment and prevention.*

***Key Words*:** Asthma, Novel drug delivery, metered dose inhaler, Dry powder inhaler, liposome, Nanoparticle, Solid lipid nanoparticle, Dendrimer

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1. INTRODUCTION

In his book entitled "On asthma and its treatment" published in 1860, Henry Hyde Salter defined asthma as peculiarly characterized paroxysmal dyspnoea that is typically periodic and separated by intervals of normal breathing [1]. Currently, asthma could be understood as a chronic inflammatory disease of the airways characterized by episodes of coughing, wheezing, difficulty in breathing, and chest tightness [2]. The impact of asthma on patients, families, and society is disproportionately high in low- and middle-income nations where access to competent treatment is limited. Despite a global decrease in asthma mortality in adults and children over the last 25 years, owing partly to greater usage of inhaled corticosteroids, there is still a significant global difference in years of life lost due to asthma [3]. Despite major advances in decoding the underlying pathogenesis, the exact series of events remain unclear hence, making it incurable. Two major reasons can be attributed to this, one, complexity in molecular mechanisms involved, and two, heterogenicity due to severity, differences in gene expression, genetic polymorphism, and variegated response to treatment [4]. Therefore, asthma refers to a general term that comprises a range of clinical presentations [5].

The most popular diagnostic treatments are mostly therapeutic agents such as antihistamines, corticosteroids, antileukotrienes, decongestants, mast cell stabilizers in the form of tablets, and sprays via oropharyngeal, intranasal, intratracheal routes, etc. However, these conventional dosage forms have some drawbacks mentioned as follows:

- To maintain the Drug Plasma Concentration, multiple doses are necessary.
- Drugs with a short half-life reduce patient compliance so repeated dosage is required.
- In the case of conventional dosage forms, a phenomenon known as the "typical peak-valley effect" or "see-saw effect" is observed due to variation in drug concentration in plasma, which hinders maintaining the ideal concentration of the medication.
- This modification may also result in over- or under-medication, both of which can have harmful adverse effects [6].

This led to the development of novel drug delivery systems, which offers advantages over traditional dosage forms, to overcome all of the above-mentioned restrictions.

2. ETIOLOGY

2.1. Genetics

It has been devised that genetics contribute to development of asthma in the range of 35%-95% [7]. The diversity in asthma phenotypes exists as a result of polygenic inheritance or varied combination of genes [8]. Multiple studies show that children with asthmatic parents are at increased risk of developing asthma [7]. For instance, the first Genome wide association studies (GWAS), published by Moffatt and colleagues in 2007 outlined that altered chromosome 17q12-21 is associated with childhood asthma [9]. Farzan et al. too showed that polymorphism in 17q21 locus enhanced the risk of

exacerbations in children despite treatment with inhaled corticosteroids [10]. Association studies also revealed that more than 100 genes were associated with allergy and asthma in 11 different populations [11]. ADAM33, an asthma gene, first recognized in Caucasian families from the United States and United Kingdom, was associated with bronchial hyperresponsiveness [12].

Table – 1: Major gene alterations identified in various asthma studies [7]

Possible functional groups	Genes
Atopy	HLAG, FCR1A, CD23, OPN3/CHML, CYF1P2, IL4, IL4RA, IL12, IL13, GATA3, STAT5, STAT6, TBX21, PHF11, IRAKM
Barrier function	FLG, SPINK5, CTNNA3, C11orf30, COL29A1, PNEDRIN, IL13
Eosinophils	MYB, WDR36, ILR1RL1, IL33
Epithelium	IRAKIM, TLR2, TLR4, CD14, GSTP1, GSTMI1,3,5, GSTT
Protein folding in endoplasmic reticulum	ORMDL3, GSDMB, ZPBPW, IKZFE
Tissue response	ADAM33, UPAR, NPSR1, IRAKM, IL13, COL29A1, TNC

2.2. Air pollution

Numerous epidemiological studies implicate air pollution as a major cause and aggravation of asthma [13]. Urbanization is, indeed, one underlying factor in the rising levels of air pollution leading to global burden of asthma and such respiratory ailments. Studies reveal those mothers exposed to air pollution had a detrimental effect in pulmonary development in utero [14]. Gaseous pollutants such as carbon monoxide, carbon dioxide, nitrogen dioxide, ozone, sulfur dioxide, heavy metals like lead, chromium, volatile organic compounds (VOC) and polycyclic aromatic hydrocarbons (PAH) are some of the significant ones [15]. NO2 in concentrations of more than 0.2ppb infiltrates deeper into the lungs and induce coughing, wheezing, bronchospasm, dyspnoea and even pulmonary edema [15]. SO2 is released from combustion of sulfur-containing coal and oil into the atmosphere [15]. Upon inhalation, it enters into the lungs, gets converted into bisulfite which interacts with sensory receptors to produce bronchoconstriction [15]. Among air pollutants, particulate matter (PM) has the greatest impact on human health [15]. PM can be defined as a complex blend of soot, smoke, dirt, dust and liquid droplets [15]. They act by activating oxidative stresses and initiate allergic inflammatory response [15]. Low-dose $PM_{2.5}$ has been shown to escalate Th-17 mediated cytokines, chemokines as well as neutrophil infiltration [16]. PM exposure may also result in apoptosis and autophagy in lung epithelial cells in asthma [15]. Diesel exhaust particle (DEP), is thought to enhance IL-33 signals in airway epithelium and aggravates severe airway hyperresponsiveness [10]. Indoor air contaminants, such as endocrine-disrupting chemicals (EDC) tend to increase parasympathetic activity that might enhance the risk of asthma [10].

2.3. Infections

One of the most common causes of Respiratory syncytial virus (RSV) infection in early life increases the risk of asthma [10]. Viruses such as rhinovirus, parainfluenza virus, coronavirus, influenza virus are associated with increased risk to development of asthma. Studies reveal that young children with severe symptoms during bronchiolitis are at increased risk of asthma [7]. Respiratory viruses significantly infect epithelial cells of the lungs [2]. In response to this, the healthy epithelial cells produce antiviral factors which aid in viral clearance [2]. However, in chronic inflammation of the airways of asthmatic patients, the antiviral response of epithelial cells become altered, leading to prolonged inflammation [2]. Such respiratory viruses could cause serious uncontrolled asthma exacerbations requiring urgent medical help and/or hospital admission [1]. It has been demonstrated using epithelial cells cultured in vivo that rhinoviruses render these cells resistant to apoptosis, thereby expanding the viral growth followed by their shedding leading to cytotoxic death of cells [1]. Single-cell RNA sequencing (RNA-seq) analysis on virus induced asthmatic patients revealed a gene core associated with IL-33 and epithelial cell repair [2].

2.4. Exposure to Allergens

More than 80% children with asthma are sensitized on exposure to environmental allergens, indoor allergen being most pivotal [17]. Allergens promote susceptibility to viral-induced wheezing [17]. The most common allergen in allergenic asthma is group-1 grass pollen [10]. Artemisia pollen allergy is a prominent cause of asthma in Northern China [10]. *Aspergillus fumigatus*, another potential allergen, is associated with reduced BAL macrophages, increased BAL levels of IL-4, IL-6, IL-10, IL-13 and TNF-α, and increased plasma levels of IL-4, IL-6, IL-10, IL-13, IL-17 and TNF-α [10]. However, no relationship between the presence of *A.fumigatus* and severity or control of the disease was established [10]. Cockroach allergens can activate the TLR2-trans-IL-6 signaling pathway in mice, which attracts neutrophils into the airways by increasing IL-17A production in CD-T cells, thereby contributing to neutrophilic asthma [16].

Examples of triggering agents in asthma:

- Allergic triggers- Pet dander, Dust mites, Pollens, Molds
- Physical triggers- Allergic rhinitis, Exercise

- Environmental triggers- Air pollutants, Tobacco smoke, Humidity, Cold air. [18]

Table - 2: List of aggravating factors in development of asthma [8]

Allergens	Airborne pollens House dust mites Animal dander Cockroaches Fungal spores
Drugs	Aspirin NSAIDs Non-selective β blocker
Emotions	Anxiety Stress Laughter
Environment	Cold air Fog Ozone Sulphur dioxide Nitrogen dioxide Tobacco smoke Wood smoke
Exercise	Particularly in cold, dry climate
Occupational stimuli	Bakers- Flour dust Farmers- Hay mould Printers- Arabic gum Chemical workers- azo dye, anthraquinone, ethylenediamine, toluene diisocyanates, polyvinyl chloride Plastics, rubber, wood workers- Formaldehyde, western cedar, dimethylethanolamine, anhydrides
Preservatives	Sulphites Benzalkonium chloride

2.5. Smoking

Noneosinophilic inflammation, with or without neutrophilic inflammation is commonly found in asthma patients associated with smoking [19]. Asthmatics who smoke tend to have uncontrolled symptoms, high risk of exacerbations, and increased emergency room visits [14]. Smoking during pregnancy predisposes to development of early onset asthma in the offspring [14]. It has been put forward that smoking during pregnancy affected lung functions more drastically than neonatal exposure [20]. In addition, exposure to tobacco smoke aggravates symptoms in a dose-independent manner [14]. It has been put forward that one puff of cigarette smoking contains 1016 oxygen radicals which activate inflammatory cells as well as growth factors and matrix metalloproteinases [20]. Smoking accelerates reduction in lung volume often linked with ageing [20]. In adults FEV1 diminishes after the age of 30 by roughly 30ml/year, whereas in smokers it is on average 40-45 ml/year [20].

2.6. Obesity

Obesity is considered to play a vital role in worsening asthma. A study on the same by Michael et al. showed that all patients who were on oral steroids were obese with mean BMI higher than those not taking oral steroids. One possible explanation could be increase in weight as a side effect of steroid therapy. Moreover, moderate to severe asthma tend to be prevalent in children who were obese [21]. Severity of the disease markedly affected the disease control and reduced response to inhaled corticosteroids. [22]. Another study by Schacter et al. Found that symptoms of dyspnea and wheezing in obese patients were often diagnosed to be suffering from asthma [21]. A recent study concluded that weight loss helped in improving asthma control in both children and adults, whereas improved lung function in adults. Further research, however, needs to be done on establishing a clear mechanism correlating obesity with asthma.

2.7. Age

Asthma is responsible for a significant rise in mortality of geriatric patients [23]. Asthma in elderly patients can be classified into two groups based on age of diagnosis of the disease [23]. "Late onset" asthma is diagnosed for the first time after the age of 65, and "early onset" persists into the older age [23]. In addition, late onset asthma patients tend to be less atopic with lower levels of serum IgE as well as reduced sputum and serum eosinophils [23]. Neetu et al. Demonstrated that rate of hospitalization of older patients were more than twice than that of young adults [24]. In their study, they also found that elderly patients suffered worse-short and long term control of asthma than young adult population [24].

2.8. Gender

In a study by Teague et al., it was found that children with asthma, irrespective of severity, were primarily male with normal body mass and lung function. However, the level of blood eosinophilia and allergen sensitization were relatively high in these patients. This was contrary to what was observed in adults in the same study, wherein regardless of severity, most asthmatics were females being more obese and airflow limitations [25].

3. TYPES OF ASTHMA

Classically, depending on the type of immune cells involved, asthma is divided into: (a) Type 2 or allergic asthma and (b) non -type 2 or non-allergic asthma [26]. Type 2 asthma is associated with T helper 2 (Th2) cell responses [2]. These cells, upon recognition of an allergen, produce type 2 cytokines IL-4, IL-5, IL-9, IL-13 [2]. This results in the accumulation of eosinophils, increased mucus production, whereas, allergen specific B-cells synthesize immunoglobulin E (IgE) [2]. This type of asthma generally begins in early life wherein exposure to allergens such as

pollen, dust, animal dander causes sensitization, but it can also be induced later in life, as seen in occupational asthma [2]. Non-type 2 asthma, on the other hand, does not involve Th2 cells or eosinophilic inflammation. It is often associated with obesity, ageing and smoking, thereby making it a late-onset disorder [2]. However, categorizing asthma in this manner is broad [2].

In response, experts established another way of classifying asthma that could aid in a better understanding of the disease. Woodruff et al. And Wenzel et al. Classified asthma into two endotypes (Th2 high and Th2 low) based on clinical features and biomarkers [16]. Endotypes are determined by underlying pathophysiological mechanisms that may result in direct variances in responsiveness to common therapy like inhaled corticosteroids or unique biologicals. Based on this, asthma can be divided into:

1. type 2-high or ultra-high (eosinophilic)
2. type 2-low (non-eosinophilic or neutrophilic) [2]

Hence, classification based on phenotypes and endotypes allows for the development of individualized and targeted medicines to address currently unmet requirements in the management and control of asthma, particularly severe asthma [27].

3.1. Type 2-high asthma

Type 2 immunity and inflammation are thoroughly researched and understood. It is distinguished by the production of type 2 cytokines such as IL-4, IL-5, and IL-13, as well as high levels of IgE antibodies. Type 2 cytokines are the primary regulators of type 2 inflammation [27]. More severe form is represented as ultra-type2-high asthma [2]. It is caused by allergen-induced IgE synthesis and Th2-associated cytokine production. IgE facilitates mast cell and basophil degranulation after allergen recognition via FcεRI cross-linking, and FcεRI activation results in the generation and release of inflammatory mediators. Eosinophil production, transport, and activation, goblet cell differentiation and mucus hypersecretion, airway hyperresponsiveness, and airway remodeling are all mediated by IL-4, IL-5, and IL-13 [16]. In response to TSLP, IL-25, and IL-33 signaling, ILC2s are activated and release type 2 cytokines (IL-4, IL-5, IL-9, IL-

13) and prostaglandins, boosting Th2-driven allergic reactions in the airways [26]. When exposed to allergens, epithelial cell-derived IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) increase ILC2 amplification and release high amounts of type 2 cytokines, boosting airway

inflammation. Although corticosteroids may treat most Th2 asthma, in some cases of late-onset eosinophilic asthma, persistent eosinophilia is noted despite high doses of glucocorticoids, and these patients often present with severe asthma [16].

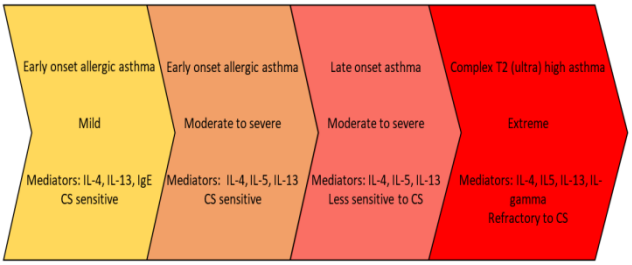

Fig -1: Progression of Type 2- high asthma [2]

3.2. Type 2-low asthma

The underlying pathophysiological mechanisms of type 2 low asthma are substantially less understood than those of type 2 high asthma [27]. The type 2-low endotype is more complex, with no biomarkers discovered thus far. As a result, type 2-low asthma encompasses all asthmatic individuals who do not have type 2-high inflammation [2]. One feature of such patients is a high amount of neutrophils (rather than eosinophils), which is generally associated with a high level of TH1 and TH17 cells. Resistance to steroid treatments is seen in neutrophilic asthma caused by TH17 inflammatory mediators, which appears to be a typical hallmark of type 2-low asthma [27].

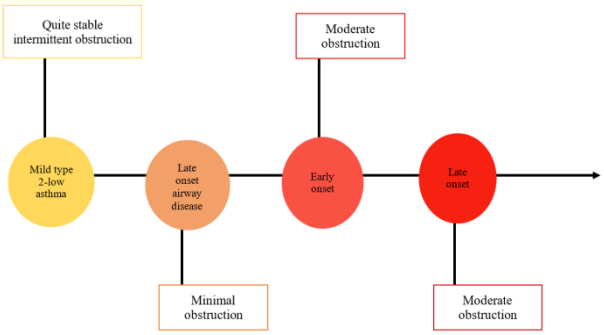

Fig -2: Progression of Type 2- low asthma [2]

3.3. Epidemic Thunderstorm asthma (ETSA)

Acute asthma exacerbations developed post-exposure to thunderstorms are referred to as Epidermic Thunderstorm Asthma (ETSA). On 21 November 2016, the most devastating epidermic thunderstorm asthma catastrophe in history occurred in Melbourne [28]. Thousands were hospitalized for severe respiratory ailments [29]. During the 12-hour storm, hospital admissions for asthma surged by over 1000%, a record breaking figure for which the health care system was unprepared [29]. Approximately 87% of the admitted patients suffered from allergic rhinitis, 28% were diagnosed with asthma, and 10 deaths have been reported [28]. Thunderstorms have the ability to bring airborne-allergens to the ground level, among which pollen grains, particularly grass pollen, are the most prominent [29]. Fungal spores may also be present in greater quantities in the atmosphere [29]. On exposure to moisture, as in rainfall, the pollen grains swell up and rupture due to osmotic shock, thereby releasing numerous fine allergenic

starch granules into the air [29]. These granules are fine enough to penetrate deep into the airways and trigger allergic responses, leading to asthma attacks in sensitized patients as well as in people without a history of asthma [29,8]. Unusual whether environmental factors brought on by climate change contribute to the global emergence of ETSA [29].

3.4. Aspirin-exacerbated respiratory disease (AERD)

Aspirin-exacerbated respiratory disease (AERD), a subcluster of Th2-high asthma, is induced by aspirin or any NSAID that inhibits the COX-1 enzyme [5,30]. This is characterized by a triad of asthma, eosinophilic rhinosinusitis, and nasal polyposis [30]. Patients with AERD are believed to have lower baseline lung function than those with aspirin-tolerant asthma, as indicated by the presence of airway remodeling [30]. When such patients ingest a COX-1 inhibitor, within 60-180 minutes an acute reaction develops involving symptoms comprising of coughing, nasal congestion, sneezing, rhinorrhea, wheezing, and fall in lung functions [30]. However, these are considered to be hypersensitivity reactions rather than allergic reactions [30]. Blocking of COX pathway redirects the arachidonate substrates to the 5-lipoxygenase pathway which produces cysteinyl leukotrienes (Cys-LTs) [31]. Mast cells, eosinophils and platelet adherent leukocytes have 5-lipoxygenase and leukotriene C4 synthase enzymes which function in the synthesis of cysLTs [31]. These cells and consequently, the cysLTs are elevated in AERD and are responsible for edema, bronchconstriction, smooth muscle hypertrophy, fibrous collagen depositions and mucus secretion into the airways [31,30]. Apart from this, patients with AERD have elevated levels of PGD2 (produced by mast cells), another inflammatory mediator responsible for extra-respiratory symptoms, particularly rashes and gastrointestinal distress [30]. In addition, eosinophils, basophils and platelets may be involved [30]. However, further research is required to understand a precise mechanism underlying the disease pathogenesis. Although rare in children, aspirin-exacerbated respiratory illness is more common in persons with severe asthma (15% vs 7% in the general population) and is typically accompanied by rhinitis and nasal polyposis [3].

4. MORPHOLOGIC FEATURES

In asthma, histopathological abnormalities in the bronchial and bronchiolar walls include the mucosa (the epithelium and lamina propria), submucosa (which includes airway smooth muscle (ASM) and mucus-secreting glands), and adventitia (the contact between the airway and the surrounding lung parenchyma). Airway epithelium seems weak in endobronchial biopsies, as evidenced by partially or totally denuded regions. Asthmatics have more epithelial cells in their bronchoalveolar lavage, indicating the possibility of epithelial desquamation in the airway lumen. This breakdown of the mechanical and biochemical dynamic barrier can result in submucosal cellular activation, which is referred to as an aberrant epithelial mesenchymal unit [32].

5. SYMPTOMS

Wheezing, shortness of breath, chest tightness, and cough are some of the symptoms of asthma. The most distinguishing elements of asthma are related to the pattern of symptoms, such as symptom kind, timing, triggers, and response to therapy. However, Exercise-induced bronchoconstriction may be the only symptom of asthma, especially when combined with high-intensity aerobic exercise, cold dry air, or chlorinated swimming pools. As a result, meticulous history taking is required to determine the likelihood that respiratory symptoms are caused by asthma rather than another diagnosis or condition [3].

6. PATHOPHYSIOLOY

As previously stated, asthma is the result of a complex interaction between genetics, environmental factors, as well as innate and adaptive immunity.

A collection of individuals with comparable clinically discernible traits are referred to as phenotypes because they lack a clear etiologic link to a particular pathophysiologic mechanism. Contrarily, an endotype describes a subgroup that exhibits the same pathophysiologic events that result in the onset, progression, and manifestation of a disease [33].

The following events play a significant role in the pathogenesis of asthma:

6.1. Inflammation

Airway inflammation is a multicellular process that involves CD4+ T lymphocytes, eosinophils, neutrophils and mast cells [34]. Although inflammation occurs largely in the airways, it may also involve terminal bronchioles and sometimes alveoli in severe cases [35,34]. The initiation of an inflammatory response in asthma begins when an allergen paves its way into the airways. Dendritic cells, which are antigen presenting cells present in the airway epithelium, assimilate these allergen with the aid of cathepsin S [35,34]. These peptides are then presented by HLA molecules (MHC class II). The dendritic cells then migrate to lymph node so as to initiate production of allergen-specific T-cells [35]. Hence, dendritic cells play a significant role in allergen-induced airway inflammation. There are roughly 500 dendritic cells per mm^2 within the epithelium [32].

6.2. T lymphocytes

By releasing particular cytokine patterns that promote eosinophil recruitment and survival as well as mast cell maintenance in the airways, T lymphocytes play a critical role in directing the inflammatory response in asthma [35]. Two subsets of effector CD4+ Th cells with distinct activities and cytokine secretion patterns were discovered and designated as type 1-Th (Th1) and type 2-Th (Th2) respectively [36]. Circulating memory Th2 cells localized in parenchyma function in eosinophil and T cell recruitment to the lung [2]. On the contrary, CD4+ resident memory T

cells (Trm) are seen in the lungs of patients with type 2-high asthma [2]. These cells release more Th2 cytokines than circulating Th2 cells and respond quickly on re-exposure to allergen albeit the mechanism is not clearly understood [2]. Trm cells induce mucus production, eosinophil activation, and bronchial hyperresponsiveness [2].

6.3. Mast cells

Mast cells are degranulated leukocytes which contain proinflammatory mediators such as histamine, proteases, lipid bronchoconstrictors such as cysteinyl- leukotrienes (LTD4, LTE4) and prostaglandins (PGD2) [37]. Although they are usually located in lamina propria in normal human airways, in asthma they are found in the airway epithelium, mucus glands and smooth muscles [32]. They are activated by allergens through IgE dependent mechanism [35]. Increased serum level of IL-33 is thought to be linked to activation of mast cells [10]. Mast cell counts are elevated in eosinophilic and Th2-high asthma, but normal in the submucosa of individuals with severe noneosinophilic asthma and the epithelium of nonsmokers with Th2-low asthma [19].

6.4. Neutrophils

The accumulation of neutrophils into the airways can cause significant tissue damage during inflammation [38]. This is because it is an inherent source of mediators such as prostaglandins, thromboxanes, LTB4 and PAF which aggravates inflammatory response [38]. Neutrophils may play a role in pathophysiology of asthma by releasing these mediators along with reactive oxygen species, enzymes namely elastase, cathepsin G, myeloperoxidases and non-enzymatic defensins [32]. Neutrophils are associated with non-allergic and steroid resistant asthma [5].

In severe neutrophilic asthma, antigen-presenting cells (APCs) encounter allergens and transport them to draining lymph nodes, where they activate naive Th0 cells. Th0 cells differentiate into Th17 cells and produce cytokines in the presence of particular cytokines (e.g. IL-17 and TNF-a). These cytokines then act on epithelial cells, promoting the release of IL-8, CXCL1, and granulocyte colony stimulating factor (G-CSF), all of which enhance neutrophil activation and recruitment. IL-8 is secreted by recruited neutrophils, exacerbating neutrophilic asthma. IL-8 is secreted by recruited neutrophils, exacerbating neutrophilic asthma. In the presence of specific stimuli, activated mucosa-associated invariant T (MAIT) and CD T cells create IL-17-secreting isoforms, which increase cytokine secretion (e.g., IFN-c, IL-17, and TNF-a), promote neutrophil recruitment, and aggravate asthma symptoms. The inflammasome (Nod-like receptor protein 3 [NLRP3]) self-oligomerizes to recruit apoptosis-associated speck-like proteins such as CARD (ASC) and pro-caspase-1. Activation caspase-1 causes pro-IL-1b and pro-IL-18 cleavage and activation, which results in a significant amount of IL-1b and IL-18 production and promotes the development of neutrophilic asthma. Certain miRNAs are secreted more often in neutrophilic asthma, and miRNAs enhance IL-6 and IL-8 production by airway epithelial cells. Asthmatics have higher exosome release, and exosomes enhance inflammatory cell activation and infiltration. They also contribute to airway remodeling [16].

6.5. Cytokines

Cytokines are a family of small glycosylated proteins that function in cell signaling, cell growth, differentiation, proliferation, chemotaxis, immunomodulation, immunoglobulin isotype switching and apoptosis [32]. Cytokines can exert their actions on adjacent cells, cells at distant sites, and cells which themselves produce them [32]. Since the functions of cytokines tend to imbricate, their individual roles in pathogenesis of asthma is arduous to characterize [32]. The cytokines which perpetuates chronic inflammatory response to asthma are those derived from T -lymphocytes [12]:

- IL-3 is crucial for the survival of mast cells in tissues and induces eosinophilia in vivo [35, 39].
- IL-4 is responsible for stimulating B lymphocytes to produce IgE, Th2 cell differentiation, enhances mucin expression on goblet cells, and expression of VCAM-1 on endothelial cells [35,39]
- IL-5 enhances eosinophil maturation and prevents apoptosis of inflammatory cells [12]
- IL-9 plays critical role in airway remodeling and eosinophilopoiesis, may mediate pathological functions along with IL-4 [12].

Apart from these, macrophages and epithelial cells too release cytokines like IL-1β, IL-6, TNF-α, and GM-CSF, which may amplify the inflammatory response [35]. Another cytokine worth mentioning is Thymic stromal lymphopoietin (TSLP), produced by airway epithelial cells and mast cells of asthmatic patients [12]. It is thought to play a significant role in stimulating dendritic cells to release CCL17 which attracts Th2 cells via CCR4 [12]. Recent studies on IL-25, IL-33 and TSLP reveal their role in initial priming of Th2 responses culminating in asthma [40]. It has been devised that IL-17 is associated with the development and severity of airway neutrophilia [41]. IL-6 is a pleiotropic cytokine produced by cells in response to inflammatory stimuli [4]. It is one such cytokine associated with neutrophilic airway inflammation [4]. It acts as an indicator of metabolic dysfunction along with asthma severity thereby making it a potential biomarker in obese asthmatic patients [4].

6.6. Eosinophils

Infiltration of eosinophils plays a prominant role in differentiating asthma from other non-infectious inflammatory disease of the airways [12]. In addition, asthma itself can be categorized into eosinophilic and noneosinophilic asthma based on presence or absence of airway eosinophils [41]. Hence, it could be inferred that eosinophils are not essential in clinical manifestations of asthma [41]. Mediators such as IL-5, granulocyte-macrophage colony stimulating factor (GM-CSF), eotaxin and CCL5 aid in the recruitment of eosinophils and lymphocytes into the airway wall of asthma patients. Their

recruitment initially involves adhesion of eosinophils to vascular endothelial cells by expression of specific glycoprotein molecules on the surface of eosinophils (integrins) and their expression of molecules such as ICAM-1 in the airway circulation [12]. They then migrate towards submucosa and subsequent activation take place [12]. The activated eosinophils release mediators near airway nerves, which changes the tone of parasympathetic and sensory nerves, thereby promoting BHR [2]. Apart from this, eosinophilic-associated fibrogenic factors such as TNF-β leads to airway remodeling characterized by smooth muscle thickening, goblet cell metaplasia and deposition of extracellular matrix protein [2]. In addition, persistent airway inflammation associated with eosinophils damages lung structural cells induced by the release of cytotoxic granule proteins (MBP, EPO, EDN) [2]. IL-5 plays a crucial role in maturation and recruitment of eosinophils into the airways [34]. Accordingly, anti-IL-5 therapy has demonstrated clinical efficacy in hypereosinophilic syndromes [41]. Recent studies on the clinical efficacy of mepolizumab, an anti-IL-5 monoclonal antibody was shown to reduce both blood and sputum eosinophil levels that reduced asthma exacerbations and facilitated reduction in oral corticosteroid therapy [41]. Eosinophils are linked to the development of AHR through the release of basic proteins and oxygen-derived free radicals [12]. Eosinophils from asthmatic patients show exaggerated responses to PAF and phorbol esters on comparison with eosinophils from atopic nonasthmatic individuals [12].

6.7. Macrophage

Monocytes and macrophages are prevalent in airway mucosa in chronic asthma [34]. Macrophages can be activated by allergen via low-affinity IgE receptors particularly FcεRII [35]. Macrophages, along with epithelial cells produce mediators such as endothelin-1, profibrotic cytokines like TNF-β and PDGF [35]. Alveolar macrophages (AM) play a defensive role in maintaining pulmonary tissue homeostasis [5]. They also phagocytose apoptotic bodies and thus diminish inflammatory response in the airways [5.]. In asthma, however, these mechanisms are altered due to which inflammation is prolonged in the airways [5]. It is evident that the IL-10 secretion and gene transcription become defective in macrophages and monocytes, which may indicate severity of asthma by intensified inflammation [35].

6.8. Airway mucus

In asthma, the airway lumen is impaired and finally gets obstructed by localized mucus aggregation under conditions that cause mucous hypersecretion, including increased mucin production and secretion, growth of gel layer, and ineffective mucous clearance [41]. Impaired mucosal clearance is a potent contributor of fatal asthma [37]. In addition, infections with bacteria can worsen mucociliary clearance, increase mucus production and lead to persistent lower airway inflammation [17]. The most prevalent mucin released by goblet cells is Muc5AC which is also responsible for generating gels in airway secretions [42].

6.9. Airway remodeling

It has been observed the occurrence of structural alterations in asthmatic patient's airways. Collagen (type III and IV) and fibronectin deposition, increased thickness of the subepithelial basement membrane, goblet cell hyperplasia, increased ASM mass and size, angiogenesis, and fibrosis are all examples of these alterations contributing to a condition known as airway remodeling [32]. The thickness of subepithelial lamina reticularis increases with increasing severity of the disease, unrelated with duration [1]. In asthma, goblet cells take the place of ciliated cells, which results in airway remodeling [37].

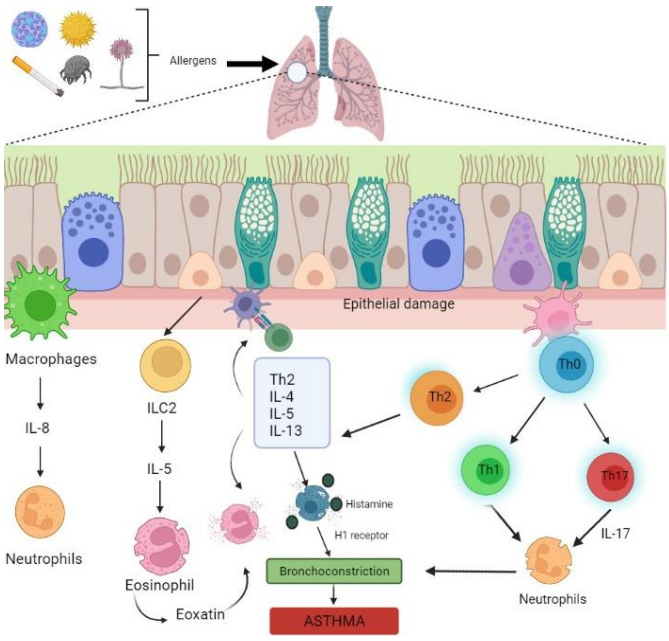

Fig - 3: Generalized pathogenesis of asthma [57]

7. TREATMENTS

As previously stated, asthma is a disease that affects airway epithelium cells, immunological cells, and various structural cell types. Details of the relationships between these cell types, as well as the interactions between currently available medicines and the host response, are being researched. Observation on the biologic reaction and the efficacy of various medicines in specific groups may one day lead to tailored therapeutics [43]. Treatment of comorbidities and modifiable risk factors, modification of lifestyle towards a healthier one by avoiding exposure to tobacco, promoting weight loss in obese patients, sublingual immunotherapy for some patients, removal from occupational exposures as well as ceasing the use of NSAIDs and inhaler training are all to be included in the individualized approach to treating asthma [3]. Medicines continue to be the mainstay of treatment, notwithstanding the importance of allergy avoidance and the control of comorbidities such as smoking and obesity. Despite modern therapy and management options, a considerable majority of asthma patients still have poorly managed illness and are vulnerable to acute exacerbations, which are mainly triggered by a respiratory viral infection. As a result,

innovative medicines to improve control and prevent asthma exacerbations remains needed. Inhaled corticosteroids β2 adrenergic receptor agonists, injectable immunoglobulin E antibodies, and quick relief medicines are used in combination treatment of asthma [43].

Table – 3: Overview of drugs used in asthma [27]

Drug	Category	Target	Mechanism of Action	Medical use	Examples
ICS (Inhaled Corticosteroids)	Long-term control medications	Glucocorticoid receptors	Suppression of airway inflammation	Mild/Moderate persistent asthma	Budesonide, beclomethasone, fluticasone
LABA (Long Acting β_2 agonists)	Long-term control medications	β_2AR	Relaxation of bronchial smooth muscle	Moderate to severe asthma	Salmeterol, formoterol, olodaterol
LAMA (Long Acting Muscarinic Antagonists)	Long-term control medications	MRs (functional selectivity for M3R)	Relaxation of bronchial smooth muscle	Uncontrolled asthma	Tiotropium, umeclidinium, glycopyrrolate
LTRA (Leukotriene Receptor Antagonists)	Long-term control medications	CysLT receptor 1	Antagonize actions of leukotrienes in the airway	Secondary option for mild/moderate persistent asthma	Montelukast, pranlukast, zafirlukast
Other leukotriene modifier	Long-term control medications	5-LOX	Inhibit the formation of leukotrienes	Secondary option for mild/moderate persistent asthma	Zileuton
Methylxanthines	Long-term control medications	Phosphodiesterase 3, adenosine receptors	Relaxation of bronchial smooth muscle	Secondary option for mild/moderate persistent asthma	Theophylline
Mast cell stabilizer	Long-term control medications	Calcium-activated potassium channels	Inhibit the release of inflammatory mediators	Mild persistent asthma	Cromolyn
Oral and intravenous corticosteroids	Quick-relief (rescue) medications	Glucocorticoid receptors	Suppression of airway inflammation	Severe asthma	Prednisolone, prednisone, methylprednisolone
SABA (Short Acting β_2 Agonists)	Quick-relief (rescue) medications	β_2AR	Relaxation of bronchial smooth muscle	Severe asthma	Albuterol, levalbuterol

SAMA (Short Acting Muscarinic antagonists)	Quick-relief (rescue) medications	MRs (no selectivity for M3R)	Relaxation of bronchial smooth muscle	Acute asthma exacerbation	Ipratropium, oxitropium
Antibodies	Quick-relief (rescue) medications	IgE and ILs	Reducing inflammation by blocking IgE and ILs	Allergic and severe asthma	Omalizumab, mepolizumab, dupilumab

8. NOVEL DRUG DELIVERY FOR ASTHMA

The term "novel drug delivery system" (NDDS) refers to the development of new pharmaceutical forms with modified properties such as lower particle size, greater permeability parameters, and selective site targeting [44]. When compared to their impact in traditional dosage forms, NDDSs can be employed to improve the performance of biotherapeutic drugs [44]. Some of the approaches that favors enhanced efficiency of asthma therapy with the aid of NDDS are described as follows:

8.1. Pulmonary drug delivery

Inhalation is a preferable route of drug administration in the treatment of asthma as well as COPD. The use of inhaled epinephrine for asthma treatment was first documented in England in 1929 [39]. Inhalational devices are classified into 4 categories: metered dose inhalers, soft mist inhalers (SMIs), dry powder inhalers (DPIs), and nebulizers. [45]. In truth, no inhalation device meets all of the requirements for delivering medications with greater patient compliance [46]. Dry powder inhalers (62.8%-88.5% of patients) and pressurized metered dose inhalers (18.9- 35.3% of patients) are most widely recommended inhalers for maintenance management of asthma and COPD [46].

Advantages of Pulmonary drug delivery:

- Enzymatic activity is relatively modest.
- Large surface area for absorption (100 m^2).
- A large vasculature.
- Short air-blood exchange channel due to weak alveolar epithelium [47].

8.1.1. Metered dose inhalers

The pressurized metered dose inhaler, often known as metered dose inhalers, is the most extensively used delivery device for medicine aerosol delivery. Metered dosage inhalers have several advantages, including mobility, the absence of an external power source, and the delivery of a set dose. pMDIs are favoured devices for administering drugs such as bronchodilators, steroids, anti-inflammatory compounds, and anticholinergics [46]. Hence, MDIs remains the most commonly used devices [45]. The pMDIs allow effective aerosolized administration of drugs. A pMDI is a pressurized system that contains roughly 1% of the total contents of propellants, flavouring agents, surfactants, preservatives, and active medicament [46]. Breath-actuated pMDIs, such as the Easibreathe® device detects the patient's breathing rate and automatically adjusts the trigger sensitivity for device activation. These are breath-controlled devices that synchronize the pace of inhalation with the release of the dose from the inhaler [46]. The issue of poor synchronization between the patient's breath and inhaler actuation can be avoided in this manner [46]. Azmacort®, which includes the inhalational corticosteroid triamcinolone acetonide, is an example of metered dose inhaler [46]. It requires a spacer device such as Aerochamber for proper administration [46]. It comes in the shape of a canister and should be thoroughly shaken before use [46]. Flovent HFA is another example of a pMDI; it has a metering valve linked to an aluminium canister and contains fluticasone, an inhaled corticosteroid suited for delivery [46]. The disadvantage of taking Flovent HFA is that it is ineffective in treating acute bronchospasm [46].

Advantages of pMDI:

- It is portable and simple to carry around [48].
- The patient's effort to inhale does not affect the amount of aerosol that is released [48].
- The inhaler canister's contents are shielded from contamination or oxidation [48].
- Suitable across age groups, with the aid of spacers or face masks [48].
- Can be used for both acute and chronic clinical conditions [48].

Disadvantages of pMDI:

- pMDIs necessitate perfect coordination between actuation and inhalation, which can be difficult, particularly in youngsters and the elderly [48].
- High oropharyngeal deposition [48].
- When delivered under pressure, the drug is at a low temperature and might induce pharyngeal discomfort [48].

8.1.2. Dry powder inhalers

Dry powder inhalers are (DPIs) yet another type of pulmonary delivery device that requires less synchronization between the actuation and breathing process to deliver powdered medications to the respiratory tract [49]. DPIs offer superior chemical stability since they

are made up of dried drugs as opposed to suspensions or solutions [49]. Dry powder is often composed of micronized medication particles in conjugation with large-sized excipients such as lactose, sucrose and glucose [49]. DPIs come in a variety of forms such as single-unit dose, multi-unit dose, and multiple reservoirs [49]. However, the formulation and production of dry powder particles with adequate properties for aerosolization and pulmonary administration is complicated [49]. Another challenge in the design of dry powder inhalers is the balance between flow rate and inhaler resistance in the device [46]. A quicker airflow is required in DPIs to promote particle deagglomeration, and greater impacts can yield a larger fine particle percentage [46]. Nevertheless, fast airflow increases the likelihood of deposition in the oropharynx and limits medication powder distribution to the lungs [46]. Depending on how reliant they are on the patient's inspiratory flow, DPIs can be either active or passive [50]. DPI formulations have been produced using a variety of standard procedures [51]. These approaches, however, have several drawbacks, including particle size, size dispersion, structure and insufficient control over powder crystallinity [51]. These issues can be resolved using specialized milling processes [51].

Table – 4: List of some common inhaler devices used in Canada [50]

Trade Name	Drug(s)	Device Type	Doses per unit	Drug Class
Onbrez®	Indacaterol	Breezhaler®	30	LABA
Breo®	Fluticasone furoate + vilanterol	Ellipta®	30	LABA+ICS
Flovent®	Fluticasone propionate	MDI	120	ICS
Ventolin®	Salbutamol	Dsikus®	60	SABA
Pulmicort®	Budesonide	Turbuhaler®	200	ICS
Spiriva®	Tiotropium	Handihaler®	30	LAMA

Advantages of DPI:

- DPI is easier to use and has benefits of enhanced medication stability and being free of propellant [52].
- DPI is suitable for drug delivery of hydrophobic formulations [52].
- Patient coordination is not required [48].

Disadvantages of DPI:

- The biggest problem with passive DPIs is the variation in inspiratory forces across patients of various ages and health conditions, which affects dose uniformity. One approach to overcome this is the use of active DPIs which incorporate internal energy sources so that dose uniformity is not reliant on the patient's inspiratory flow rate [49].
- Oropharyngeal deposition resulting in adverse effects such as oral candidiasis [48].
- It is vulnerable to both ambient humidity and exhaled air which might reduce DPI's efficiency [48].

8.1.3. Soft mist inhalers

These are the devices that create a soft mist of aerosol for the patient to inhale without using propellants [48]. They have the qualities of both pMDIs and nebulizers, with the liquid drug in is administered at a slower pace than a pMDI [48]. Soft-mist inhalers have a great rate of deposition (approximately 35-50%) than pMDIs, according to studies [48]. Respimat® 1 Soft MistTM inhaler (SMI) is a new, propellant-free inhaler designed to enhance inhaled drug over pMDIs or DPIs [53]. The major aims of designing the Respimat® SMI were to prevent the usage of propellants, lower the amount of inspiratory effort required by the patient, increase drug administration, and improve patient compliance [54]. These are currently unavailable in India [48].

8.1.4. Nebulizers

Nebulizers are devices that produce aerosol particles ranging in size from 1-5µm for inhalation based drug delivery [49]. There are two types of nebulizers that are often used based on the type of force to create aerosols from liquid suspension/solution: jet nebulizers and ultrasonic nebulizers [49]. Jet nebulizer operates by harnessing the gas flow from a compressor [46]. The formulation is atomized through a tiny opening in the nebulizer through which the gas travels [46]. Because of the leakage, there may be considerable loss of aerosol particle during exhale [46]. Ultrasonic nebulizers are often favored for aerosol treatment because they offer a higher production capability than jet nebulizers [46]. Aerosolized particles are generated using high frequency ultrasonic waves, with the needed vibration falling within the range of (1.2-2.4 MHz) of a piezo-electric crystal [46]. Mesh nebulizer is a novel nebulizer having a mesh of numerous small holes through which the medicine is fed to produce the desired aerosol [48]. These are further classified as static mesh nebulizers or vibrating mesh nebulizers [48]. The liquid drug is pushed through the mesh holes to form the aerosol in static mesh or passive mesh nebulizers [48]. On the other hand, in vibrating mesh or active nebulizers, a piezoelectric device causes vibrations, which force the drug through the mesh [48]. An example of vibrating mesh nebulizer is Aeroneb®Go [46]. Mesh nebulizers may deliver

both liquid medication formulation and suspensions; however, the performance of suspensions appears to diminished in terms of mass of inhaled aerosol and the output rate [46]. Akhuemokhan et al. developed a microemulsion (ME) of fluticasone propionate (FP) for pulmonary administration using mesh and jet nebulizers and compared it to the drug's commercial nebulizer suspension (Flixotide® nebules) [55]. The drug was administered well by the jet nebulizer, however the microemulsion was not delivered by mesh nebulizer [55]. These promising findings were demonstrated by the aerodynamic particle size distribution created by microemulsion using jet nebulizer [55]. The formulation and the device are both critical for the effective use of the nebulization system for pulmonary targeting [46].

Advantages of nebulizers:

- Nebulizers can deliver a rather high dose to the lungs which can be useful for respiratory disorders requiring high doses [52].

Disadvantages of nebulizers:

- High oral deposition [48].
- Nebulizers typically require 15-20 minutes for drug delivery [48].

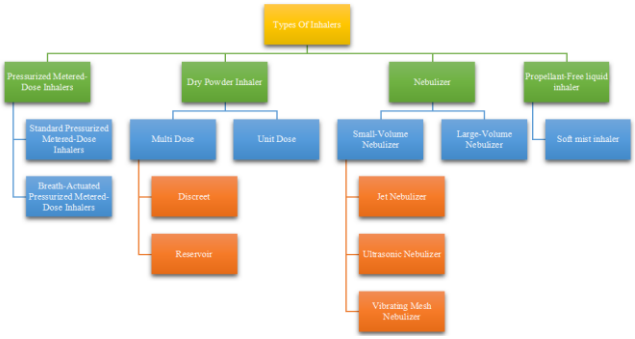

Fig -4: Types of inhalers

8.2. Particle-based drug delivery

Conventional drug therapy is typically hampered by low drug penetration and treatment response. To address this, nanoscale carriers have been employed as an advanced method to enhance pharmacokinetics of medicinal drugs. Nanoparticles, with particle size ranging from 1-100nm, are a novel technique of medication delivery [55]. These are generally intended to enhance encapsulated medication biodistribution by delivering them more effectively and selectively to the pathogenic site, also known as site-specific drug delivery [56]. The goal of this method is to improve therapeutic effectiveness while decreasing chemical toxicity [56]. Nanoparticles (NP) are classified into two types depending on their chemical composition: organic NPs and inorganic NPs [57]. Liposomes, polymeric NPs, dendrimers, and micelles are examples of organic nanoparticles, whereas inorganic nanoparticles include iron oxide NPs, gold NPs, silica NPs, quantum dots, graphene oxide, and carbon nanotubes [57].

Advantages of nanoparticles:

- The potential of nanoparticle systems to deliver targeted drugs is its primary benefit as a carrier vehicle [52].
- Nanoparticles have been employed in gene therapy to inhibit Th2 transcription factors, cytokines, and to increase the production of Th2 antagonists [58].
- Helps to enhance efficacy of existing therapies with minimal side effects [58].

Disadvantages of nanoparticles:

- Alveolar macrophages are monocyte-derived phagocytic cells that are prevalent in the lungs. Because of their small size, NPs can penetrate deep into the lungs and settle in the alveoli, where they can be consumed by macrophages. As a result, the half-life of drug-loaded NPs within the alveoli can only be a few hours, resulting in limited therapeutic efficacy and increasing dose frequency. [52].
- Distribution of NP into the lungs is difficult because their size does not allow for deep lung deposition and are hence primarily expelled through the respiratory system [52].
- Validating NP performance in vivo remains difficult. This is most likely owing to a lack of understanding of how NPs interact with complex physiological components such as pulmonary surfactants, phospholipids, and proteins in the lungs. For example, opsonin proteins found in blood serum bond to the surface of NPs, which makes them "visible" to immune cells [52].
- High production cost [49].

Some of the NPs significant in the treatment of asthma are described as follows:

8.2.1. Liposomes

Liposomes have sparked interest as a viable alternative to oral delivery for treating respiratory illnesses such as asthma since they are noninvasive and provide long-lasting therapy [57]. These are colloidal drug delivery methods made up of a lipid layer encircling an aqueous core [6]. Liposome size range from 50-100nm, depending on the cholesterol and phospholipid content [58]. The drug is distributed according to its solubility in the hydrophilic core or lipid layer [6]. Tahara et al. Developed egg phosphatidylcholine/cholesterol liposomes loaded with short acting pulmonary β2 agonist, which displayed a long term bronchoprotective effect (over 120 minutes) in a histamine induced guinea pig model as compared to the drug alone [52].

Budesonide encapsulated in stealth liposomes effectively reduced inflammation in experimental asthma, according to a study by Konduri et al. The animals accepted the treatment well and had no negative side effects. Stealth liposome encapsulation is therefore a safe and effective

vehicle for delivering inhaled steroids to the asthmatic lung [59].

An anti-asthmatic study of liposomal R-TBH conducted in guinea pigs showed that R-Terbutaline Hydrochloride (R-TBH) liposomal aerosol exerted anti-asthmatic effect 4 hours after administration, whereas no anti-asthmatic effect was observed with R-TBH. Encapsulation of R-TBH in liposomes likely protected the drug from rapid metabolism, and effective amounts of R-TBH released from liposomes were available in the lung. It was shown that sustained release of R-TBH from liposomes was achieved for at least 4 hours in vivo [60]. In a guinea pig asthma model, researchers used liposomes to treat the disease in vivo. Procaterol hydrochloride (PRO), a pulmonary β2-agonist with a short half-life, was encapsulated in liposomes and administered to the lungs. Liposomes improved drug retention in the lungs [47].

Advantages of liposomes:

- Non-toxic.
- Non-immunogenic.
- Biodegradable [6].
- Ability to incorporate wide range of active drugs.
- Ability to enhance bioavailability.
- Prevent rapid plasma clearance [61].

Disadvantages of liposomes:

- Tendency to form agglomerates [61].
- Susceptible to light, temperature, and metal ions [61].
- Difficult to sterilize [61].
- Limited potential to retain drugs for prolonged time. It can be resolved with hybrid LIP formulations [47].

Liposomes are unable to survive the shear force generated by the nebulizer; hence, physical stress is imparted to the liposomal bilayer when the aqueous dispersion is transformed into the respirable aerosol formulation. This results in the loss of the entrapped drug; however, SLN-based formulations can circumvent this [55].

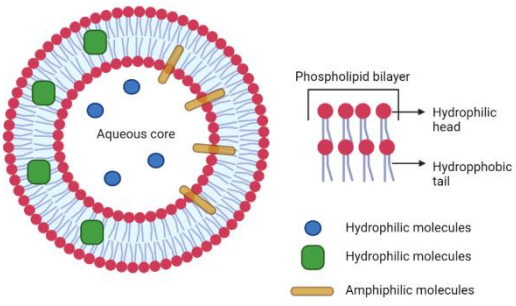

Fig -5: Generalized structure of liposomes [61]

8.2.2. Dendrimers

Dendrimers are branched macromolecules with well-defined structures [62]. They have three unique structural components: a core, interior layers made up of repeating units, and functional terminal groups [62]. Dendrimer-conjugated methyl prednisolone has been shown to improve methyl prednisolone's ability to attenuate allergen-induced inflammation [57]. In a study by Nasr et al., the solubility of poorly soluble drug beclomethasone dipropionate (BDP) was enhanced by complexing with PAMAM dendrimers [63]. The prolonged release profile, as well as the high aerosol production and Fine Particle Fraction(FPF) of BDP, imply that dendrimers are a potential nanocarrier system for pulmonary administration of BDP employing air-jet or vibrating-mesh nebulizers [63].

Advantages of Dendrimer:

- Improved cell membrane permeability [58].
- Improved bioavailability [58].

8.2.3. Solid lipid nanoparticles

Colloidal drug carriers with diameters ranging from 50nm to 1µm are known as solid lipid nanoparticles (SLN). They are composed of solid lipids or combination of liquid and solid lipids stabilized with the help of an emulsifier. The lipids often employed in the manufacture of SLN include biocompatible lipids such as waxes, fatty acids, triglycerides, and steroids that are well tolerated by the body [49].

It has following advantages:

- Ability to deliver both hydrophilic and lipophilic drugs.
- Enhanced drug stability.
- Relatively resistant to enzymatic degradation.
- Better drug delivery to the target site.
- Improved pharmacokinetic action [6].

Wang et al. used the solvent-injection approach to create curcumin-loaded SLN, which was then examined in ovalbumin (OVA)-induced asthma mice. The size of the optimized nanoparticles-based formulation was 190 nm, with a zeta potential of -20.7mV, and curcumin entrapment was determined to be 75%. Pharmacokinetic experiments were carried out in an allergic asthma model caused by ovalbumin. In the instance of SLN formulations tested in rats, a significant quantity of curcumin was identified in the lungs and liver. Curcumin-loaded SLNs inhibited T-helper-2 type cytokines, interleukin-4 and interleukin-13 significantly in vivo. In compared to curcumin alone, SLN-based formulations demonstrated active reduction of hyperresponsiveness and inflammatory cell infiltration. The study demonstrated that SLN-based formulations were superior delivery system techniques for the treatment of asthma [55].

6.8.3 Mucoadhesive drug delivery

Mucoadhesive drug delivery is mediated by the interaction of the mucus layer over the mucosal epithelium, mucin moieties, and polymer/co-polymer with prolonged dose residence time to the site of absorption [55]. The mucosa has a high blood supply and allows for quicker medication absorption than the oral route. Since it offers the chance to prevent either drug degradation by gastrointestinal contents or hepatic first-pass inactivation, pharmaceutical features of mucoadhesion have attracted a lot of attention in recent years [64].

Zhang et al. created mucoadhesive DDS-based budesonide in chitosan microparticle and assessed the characteristics of drug release in a mice model induced with allergic asthma by measuring the levels of IL-4 and IL-5 in bronchoalveolar lavage as well as mRNA [55]. The results of this study showed that, depending on the molecular weight of chitosan, drug release persisted for 12-18 hours [55]. Additionally, eosinophil number and IL-4 IL-5 mRNA levels were shown to decrease following a course of therapy lasting seven days in a row [55]. Another study reported that a mucoadhesive buccal patch containing 5 mg of Montelukast Sodium prepared by using Eudragit RL 100, and HEC, and Na CMC (F3 and F6 formulations) were best formulations [64]. these formulations of mucoadhesive buccal patches showed moderate swelling, convenient resident time, greater therapeutic efficacy, improved bioavailability and hence, turned out to be a promising one as a controlled drug delivery [64].

In a study by Lee et al., when theophylline was delivered intranasally as a complex with thiolated chitosan nanoparticles (TCN), the number of eosinophils in BAL fluid was greatly reduced primarily by inducing apoptosis or by preventing their migration. These outcomes unequivocally proved that chitosan nanoparticles delivered theophylline more effectively than unaltered chitosan or theophylline alone. One probable explanation could be the higher mucoadhesiveness of TCN is likely what caused theophylline to have stronger anti-inflammatory effects [42].

Drug delivery over mucosal surfaces have following benefits:

- Avoidance of first pass metabolism.
- Quicker absorption than oral administration.
- Drug localized at target site.
- Less expensive compared to injections.
- High patient compliance [65].

9. CONCLUSIONS

Asthma is one of the chronic respiratory diseases with a rising global burden. This demonstrates the ongoing need for new therapies. This also necessitates a thorough knowledge of the exact events taking place in the progression of the disease. While a recent breakthrough in nanotechnology has made treatment of a variety of potentially fatal lower respiratory tract infections possible, there is a need of addressing their limitations in clinical practice. This review aims to emphasize the superiority of novel drug delivery therapeutics over conventional ones, which may prove to be a more significant and prominent approach in the near future.

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