Application of NSAIDs in the Treatment of Pulmonary Diseases- a Comparative Study of the Therapeutic & the Adverse Impacts

By

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A thesis submitted to the Department of Pharmacy in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy (Hons.)

Department of Pharmacy
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Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I have acknowledged all main sources of help.

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Approval

The thesis/project titled “Application of NSAIDs in the Treatment of Pulmonary Diseases- An Overview” submitted by Farhana Rahman (15146006) of Spring 15, has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy (Hons.) on August 2019.

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Ethics Statement

The study does not involve any kind of animal trial and human trial.

Abstract

This review mainly focuses on the comparative study of both the therapeutic and adverse impacts of NSAIDs for pulmonary disorders. NSAIDs are being used by almost 30 million of people on a regular basis not only for their efficacy in reducing pain and inflammation but also pulmonary disorders like CF, COPD, NSCLC etc. having the association of high risk factors with asthma patients, SCLC, PE, pleuropulmonary complications and pregnant and breast feeding women. All the data being used in this review has been taken from published research paper, articles in the reputed journals and research databases like pubmed, sciencedirect, scopus etc. To ensure more efficient and better treatment opportunity continuous research, desensitization techniques, new dosage form and technologies are required. Considering all the potential benefits of using NSAIDs, approaches for targeted pulmonary route of administration would be the key to balancing the risk and benefits of NSAIDs for pulmonary diseases.

Keywords: NSAIDs; Pulmonary diseases; Pulmonary administration; Therapeutic effectiveness; Adverse impacts; Better & safe treatment opportunities.

Dedication

Dedicated to my parents

Acknowledgement

I would like begin by thanking the Almighty Allah, our creator, the source of our life and strength, our knowledge and wisdom, for the blessings and mercy. All praises to the Almighty Allah and I would like to express my gratitude for blessing me with immense patience, strength, gratefulness and assistance when necessary to complete this project. This research would not have been completed without the support of the people who are gratefully recognized here.

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List of Acronyms

NSAID	Non-steroidal Anti-inflammatory Drugs
OTC	Over the Counter
CF	Cystic Fibrosis
COPD	Chronic Obstructive Pulmonary Disorder
SCLC	Small Cell Lung Cancer
NSCLC	Non-Small Cell Lung Cancer
PE	Pulmonary Embolism
COX	Cyclooxygenase
AERD	Aspirin Exacerbated Respiratory Disease
DPI	Dry Powder Inhaler
BCS	Biopharmaceutics Classification System
GIT	Gastrointestinal Tract
FPF	Fine Particle Fraction
CDC	Centers for Disease Control and Prevention
FEV1	Forced Expiratory Volume in 1-Second
FVC	Forced Vital Capacity
AECOPD	Acute Exacerbations in Chronic Obstructive Pulmonary Disease
LOS	Length of Stay
ARDS	Acute Respiratory Distress Syndrome
CI	Confidence Interval
HR	Hazards Ratio
AIA	Aspirin-Induced Asthma

ASA	Aspirin Sensitive Asthma
OR	Odd Ratio
LRTI	Lower Respiratory Tract Infections
CAP	Community Acquired Pneumonia
WHO	World Health Organization
GP	General Practitioner
ICU	Intensive Care Unit

Chapter 1

Introduction

1.1 Background

Around 30 million of people are using NSAIDs every day on a daily basis throughout the whole world (Szabo-revesz, 2018) due to their efficacy for reducing pain and inflammation. (Laine, 2001). NSAIDs are recognized as the most prescribed and self-medicated group as being used by the people of different groups of age and gender due to different etiologies of pain, fever, inflammation (Tharakan, Senthilraja, & R, 2016). Biological effects of NSAIDs has been explained by cyclooxygenase (COX) enzymes' suppression, responsible for prostaglandins' biosynthesis which act by the promotion of pain as well as inflammation. COX compounds have 3 isoforms, in most healthy tissues COX-1 being expressed constitutively, while COX-2 is evolved in inflammatory cells due to the reaction of pro-inflammatory stimuli in an inducible form like injury, tumor promoting agent, bacterial endotoxins, etc. (Szabo-revesz, 2018). COX-3 isoform (variation of COX-1) has been newly discovered is being produced predominantly in brain cell (Chandrasekharan et al., 2002). Depending on their selectivity, NSAIDs are classified into three classes- nonselective COX- 1 and COX-2 inhibitors, COX-2 inhibitors having selectivity of (5 to 50-fold) & COX-2 inhibitors containing selectivity of (greater than 50 fold) . NSAIDs are additionally classified based on chemical structures &function of anti-inflammatory (Asirvatham, Dhokchawle, & Tauro, 2016). COX inhibitors which are non-selective comprise acetylsalicylic acid, naproxen, indomethacin, diclofenac etc. These are identified as analgesics having a history for acute and chronic pain like headache, postoperative pain, migraine, menstrual pain etc. Moreover they are used as antipyretics for fever, and in the case of rheumatoid diseases being used as anti-inflammatory. Nimesulide, etodolac & meloxicam these were being used as first NSAIDs those have a safety profile and

utilized as potent anti-inflammatory drug and afterward being accepted as preferential COX-2 inhibitors (Szabo-revesz, 2018).

1.2 Rationale of the Study

Being indemnified as both the prescription and self-medicated group, NSAIDs are widely used by different types of patient's among the whole population. NSAIDs are being used frequently for the management of pain, fever, inflammation with having different etiology, by different age groups due to their easy accessibility and availability in the market. As, a large group of NSAIDs are exposed to a large population, makes them a serious cause of various unwanted adverse reactions. Considering all the adverse impacts, the main concern of conducting the review is to make a comparative study among the risks and benefits of using NSAIDs in the treatment of Pulmonary diseases and providing some possible approaches to make a better and safer pulmonary route of administration by overcoming all the adverse impacts. Researchers and formulation scientists are also continuously investigating to establish a therapeutically beneficial targeted pulmonary dosage form.

1.3 Aim

This review mainly focuses on the comparative study of both the risks and benefits of using NSAIDs for pulmonary diseases.

1.4 Objectives

The objective of this study signify the following things-

- To study the therapeutic benefits of NSAIDs for pulmonary diseases.
- To study the adverse impacts of using NSAIDs in the pulmonary disorders
- To find out the possible approaches of NSAIDs for targeted pulmonary administration

1.5 Effects of NSAIDs for Pulmonary Diseases

Table 1: Using NSAIDs for pulmonary Diseases

Therapeutic effect	Adverse effect
➢ People around 95% with asthma can be treated with NSAIDs like ibuprofen and combination of drugs containing ibuprofen safely (Carter, 2017). ➢ Only NSAID that has become approved for chronic use in Cystic Fibrosis (CF) is either inhalable ibuprofen or the combination of drugs containing ibuprofen. and also the burden of CF community be reduced (Mogayzel et al., 2013; Sheikh, Ong, Pozzoli, Young, & Traini, 2018). ➢ Aspirin potentially gives therapeutic effect on chronic obstructive pulmonary disease in Chronic Obstructive Pulmonary Disease (COPD) patient because of its antiplatelet therapy (Harrison et al., 2014; Hermansson & Stro, 2013). ➢ The inhaled dose of Meloxicam is considered for the combination therapy for non-small cell lung cancer (NSCLC) & also celecoxib, rofecoxib have effective pulmonary effect (Evans & Kargman, 2004; Ishida et al., 2003). Non aspirin NSAIDs can be used for small cell lung cancer (SCLC).	➢ Around 5% of people are highly sensitive to NSAIDs (aspirin) and induce (AERD or ASA triad) which can cause life threatening issue also can trigger symptoms of asthma or allergy (nasal congestion, runny nose, cough, wheezing, breathing problems, bronchospasm, tightness in your chest, skin rash, hives, facial swelling, abdominal pains, shock) (Carter, 2017). ➢ Aspirin-exacerbated respiratory disease (AERD) causes by aspirin and other NSAIDs induced respiratory reactions in practice with sinusitis, asthma and chronic rhinitis (Goto, 2018). ➢ Prolong use of NSAIDs (aspirin) induces SCLC risk among the women and smokers (Brasky, Baik, Slatore, Potter, & White, 2012). ➢ (Two to three) fold increase in the risk of venous thrombosis and pulmonary embolism (PE) has been found to be associated with the use of NSAIDs (Huerta, Consuelo, Johansson, SAGA, Wallander, & Rodriguez, Garcia, Luis A, 2015). ➢ NSAIDs abuse in primary stages of community acquired pneumonia has been found to be associated with a blunted presentation, course of protracted

Therapeutic effect	Adverse effect
	infection together with increasing risk of pleuropulmonary complications, particularly pleural empyema (Messika et al., 2014; Voiriot, Guillaume, Dury, Sandra, Parrot, Antoine, Mayaud, Charles, & Fartoukh, Muriel, 2011). ➢ High dose of NSAIDs are not safe in the pregnant or breastfeeding women having any kind of pulmonary disorders this can cause premature closure of ductus arteriosus and pulmonary hypertension in newborn (Risser, Donovan, Heintzman, & Page, 2009).

From the Table 2, it can be said that NSAID treatment is suitable but having measured the risks versus benefits of treatment, guarantee that the patient's history is known prior to an NSAID is prescribed.

1.6 Possible Approaches of NSAIDs for Making Targeted Pulmonary Route of Administration

Tablets and capsules are the two mostly used dosages form of NSAIDs. There are some other well-known dosages form like IV, topical and transdermal system for NSAIDs (Szabo-revesz, 2018).

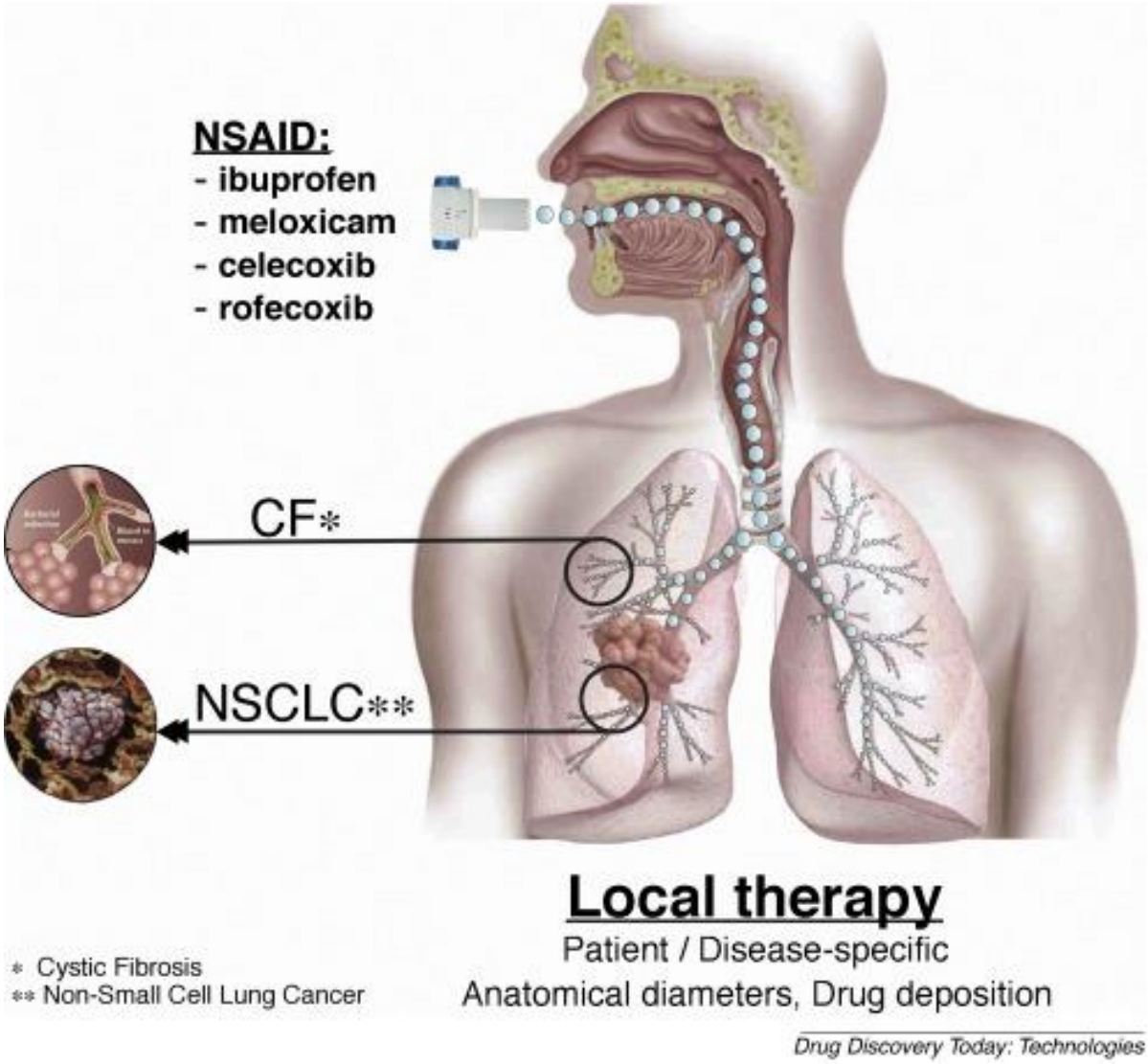

Figure 1: Pulmonary delivery of NSAIDs for respiratory disorders (CF & NSCLC) (Szabo-revesz, 2018).

New approaches of therapeutic potential are becoming significant for nasal and pulmonary application (Szabo-revesz, 2018). Recently the approach of pulmonary route of drug delivery is seeking a greater importance in the research field due to the ability of directly targeting the drug delivery to lung, besides for local and systemic treatment this is a non-invasive drug delivery approach (Patil & Sarasija, 2012). It also lowers the dose of the drug in the comparison of oral or parenteral administration. In the early 1990s, the COX-2 isoform was discovered and COX-2 inhibitors, for example, celecoxib, etoricoxib & rofecoxib having high selectivity & an expanded inhibitory impact were endorsed. These agents were explored in a few inflammatory

conditions, for example, non-rheumatoid irritation, cystic fibrosis rheumatoid joint inflammation, osteoarthritis, and non-small cell lung malignancy treatment and counteractive action (Rao, Meena, & Rao, 2005) (Figure 1).

Table 2: Biological & physiochemical properties of NSAIDs that should be considered for pulmonary route of administration (Pomazi, Ambrus, Sipos, & Szabo-revesz, 2011; Szabo-revesz, 2018)

Biological properties	Physiochemical properties
➢ Mucociliary clearance	➢ LogP
➢ Enzyme activity	➢ Solubility
➢ Permeability	➢ Dissolution rate
➢ Rheological characteristic (mucus)	➢ Density
➢ Mucus thickness	➢ pKa
➢ pH	➢ Distribution of particle- size
➢ Lung development	➢ Aerodynamical properties of drug particles
➢ Cell types per lung region	
➢ Cell growth	➢ Products dosage form (solution or DPI)

The main benefit for pulmonary route of administration includes from (Table 1), the large surface area of 0.8 m^2 conducting airways , to have a successful local therapy, to limit the diffusion of drugs into the systemic circulation minimizing side effects, to make it non-invasive and have to have therapeutic effect while being easily administered with good compliance. NSAIDs are appropriately solvent at pH 7.4 of the lungs therefore pH should be maintained, offering a better therapeutic impact. NSAIDs are likewise ideal to be inhaled since they contain molecular weight that is small and a comparatively high log P value (Pomazi et al., 2011; Szabo-revesz, 2018). There are some issue we need to ensure to increase the deposition as well as the bioavailability of NSAIDs for the formulation of pulmonary dosage form, from (Table 1) they are a controllable morphology of drug particles (size &surface), finely distributed particle size, low bulk density of particles (solid), aerodynamical property of

particles that is ideal, a fine particle fraction that is high, a mass median aerodynamic diameter which is small and an emitted dose that is high, as particle size determines the location of drug deposition and aerodynamical properties of particles determines pattern for drug deposition throughout the human respiratory tract. After the successful deposition of drug particles in the lung, the drug particles must be dissolved into the fluid of the epithelial lining. The dissolution rate is highly dependent on formulation of drug, physiochemical properties and physiologic factors. Dosages form could be liquid or Dry Powder Inhaler (DPI) depending on the patience physiology just as long residence time being given by specialist of mucoadhesive. Bioavailability of deposited drugs depends on deposited lung dose and lung specified clearance process that is achieved through mucociliary clearance. In patients, mucociliary clearance can be reduced due to high thickness of mucus layer or high viscosity of mucus. Mucociliary clearance is very complex and depends on formulation and characteristics of drug and patients. To get a better and faster effect different additives (surfactants, polymers, etc.) are being used (Szabo-revesz, 2018).

As NSAIDs are being used by a large population, this also makes them the second cause of unwanted reactions in particular there are some risk factors that the professional should understand and inform the patient while prescribing with NSAIDS for pulmonary disorder or associated diseases. NSAIDs can cause wide-ranging adverse reactions to drugs that can be clinically interpreted in different manner. Physicochemical properties of NSAIDs influence the therapeutic applications**.** In the event of respiratory application, altering the physicochemical properties of NSAIDs isn't sufficient alone, in light of the fact that the pathologic condition of lung requires extraordinary detailed formulation to guarantee a targeted anti-inflammatory impact on in CF, NSCLC and other pneumonic infections as well (Szabo-revesz, 2018). Continuous research efforts are required for the improvement in pathophysiology and the event called “silent desensitization” treatment alternative and possibly anticipation that are

considered necessary for the improved management. For the better understanding of functional and genetic/ epigenetic pathogenic mechanisms, it will be helpful in the innovation and development of new diagnostic methods and efficient management in case of pulmonary route of administration (Tharakan et al., 2016).

Chapter 2

Therapeutic effects

2.1 Use of Ibuprofen in Asthma Patient

Ibuprofen, {(±)-2- (p-isobutyl phenyl)} is a derivative of propionic acid. It belongs to class II of the Biopharmaceutics Classification System (BCS) of drugs, which is a NSAIDs (Bakhbakhi, Alfadul, & Ajbar, 2013; Bolten, Lietzow, & Türk, 2013). An over the counter medication (OTC) being used most widely to reduce pain, fever and inflammation (Carter, 2017). Mechanism action of ibuprofen is well established in various therapeutic purposes. Thus ibuprofen has therapeutic effectiveness in the treatment for pulmonary diseases like CF, asthma, COPD and many other clinical conditions either directly or indirectly. As ibuprofen is poorly soluble drug the pulmonary route administration avoids the metabolic destruction in the liver, losses of drug in GIT and supply beneficial effect over the administration of oral route. Pulmonary route may become a promising and efficient way for the drug delivery in a systemic way (Boldyrev et al., 2009). Pulmonary drug delivery system is non-invasive and provides ease of administration compared to other route of administration like oral, intravenous. Inhalable form of ibuprofen is associated in reducing the gastrointestinal adverse events so several investigations are going on establishing the inhalable formulation of ibuprofen.

Table 3: Characteristics of ibuprofen that should be considered with the physical variables to influence an efficient respiratory formulation(Irvine, Afrose, & Islam, 2018).

Characteristics of inhalable ibuprofen	physical variables
➢ High rate of deposition in respiratory tract ➢ High emitted dose ➢ Type of formulation ➢ Fine particle fraction (FPF)	➢ Breathing pattern of patient ➢ Inhalation rate ➢ Inhalation device, ➢ Independent inhalation flow rate

From Table 3, this can be said that, the geometry of the respiratory tract, mode of delivery being used, formulation of drug and the delivery device used all these factors heavily influenced the quantity of drug being deposited in the respiratory site (Irvine et al., 2018).

The high dose of ibuprofen is not always appropriate for lung delivery; it requires development of inhalable formulation with the combination of a variety of excipients. Pulmonary route provides more convenience to administer drugs those are poorly water-soluble like ibuprofen, with many challenges for the formulation scientists (Afrose, 2017) to reduce the adverse impact of taking medication through oral route and for this researches are going on.

Asthma is one of the chronic diseases of bronchial tubes, the airways carrying air into and out of lungs. About 95 percent of people with asthma can take NSAIDs like ibuprofen safely (Carter, 2017). Centers for Disease Control and Prevention (CDC) stated that, around 27 million Americans having asthma that is one of the most common chronic conditions. 1 out of every 12 children in America has this disease. Symptoms of asthma occur when the airway lining get swelled and the muscles in that region tighten. Airways get filled by mucus, diminishing the air that can pass through causing asthma assault (Sullivan, 2018).

Some people with asthma are overly sensitive to NSAIDs like ibuprofen; people with NSAIDs sensitivity are strictly restricted from taking ibuprofen having asthma, as it can worsen the asthma condition. An investigation found that the ibuprofen treated kids had fundamentally less requirement for doctor visits for asthma and this advantage was most prominent with the higher dose of ibuprofen (Levy & Volans, 2001). The study presumed that there might be some advantageous impact of the ibuprofen of being anti-inflammatory in children having asthma and there was no expansion in adverse events in the children who were being treated with ibuprofen as indicated by Lesko and Allen (Levy & Volans, 2001). Ibuprofen has important role in the treatment of NSCLC, CF and in asthma patient having no NSAIDs sensitivity. No

confirmatory human clinical data is available for ibuprofen as it is being administered orally due to the purpose of treating pulmonary/ respiratory diseases under the supervision of physician as inhalable dosage formulation of ibuprofen has not been developed yet to overcome all the negative impact.

However, formulation scientists are investigating a promising prospect to develop inhalable formulation by using nano-technology (Afrose, 2017). More studies are required, particularly in pulmonary applications, as by pulmonary administration it is possible to generate therapeutically low doses consistent dosage form to overcome the boundaries of currently existing dosage forms.

2.2 Use of Ibuprofen in the Patient of Cystic Fibrosis (CF)

Cystic Fibrosis, a genetic disorder which is identified by assembling of thick and sticky mucus in lungs, it can also cause damage to other organs like liver, pancreas, kidneys, intestine etc. It has been evaluated that, from Northern Europeans, one individual out of 25 is a transporter of a CF gene and one child out of each 2500 born is influenced (Rosenstein & Cutting, 1998) around 70,000 -100,000 people worldwide have CF (Nancy, 2016).

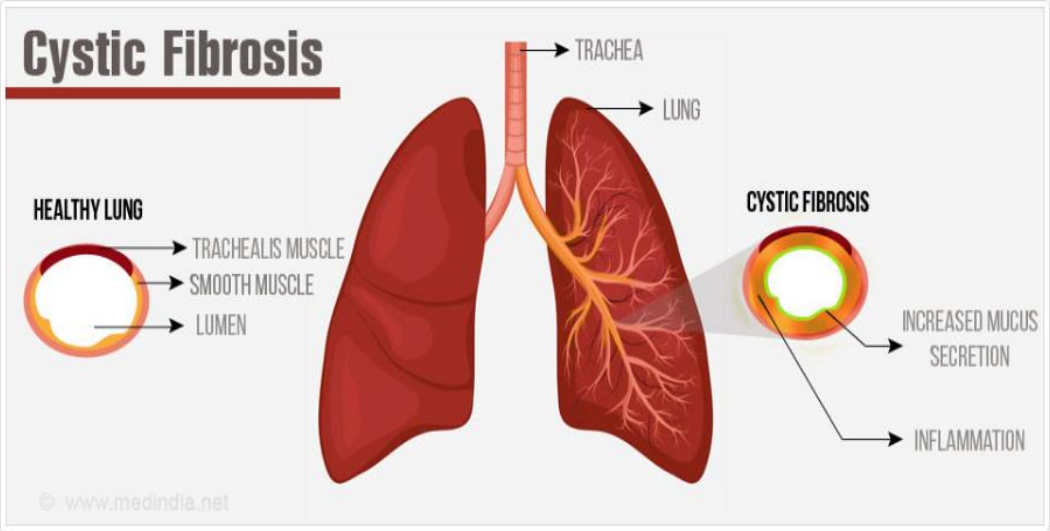

Figure 2: Comparative visualization of healthy lung and lung affected by Cystic Fibrosis (CF) (Venkataraman & Shroff, 2016)

CF mucus containing, smaller amount of water and mucin with the formation of a unique cross-linked like structure that causes high viscoelasticity and cause clogging in the airway (Figure 1). According to the report of Ruge et al. the pore size of CF mucus falls into the nano size extend. To treat CF, permeation of pulmonary drug is required through the porous sticky layer of mucus (Ruge, Kirch, & Lehr, 2013). Inhalable nano-structured particles of NSAIDs like ibuprofen (<1000 nm) is the most appropriate choice which is being investigated by the formulation scientists for the treatment of CF by effective penetration (Muralidharan, Malapit, Mallory, Hayes, & Mansour, 2015). NSAIDs must be consistently distributed throughout the alveolar tissue and airways, containing a lot of inflammatory cells (Pressler, 2011). There are a lot of NSAIDs that have been investigated for inhalation (Onischuk et al., 2016) but among them ibuprofen (per os) is the only NSAID that has become approved for the chronic use in CF, as ibuprofen works by slowing down the growth of lung disease in children (Mogayzel et al., 2013).

Two large-scale trials of high doses ibuprofen has been taken place in CF patients (Konstan, 2008; Lc & Stanojevic, 2007).

Table 4: Kostanand colleagues reported a clinical trial in 1995 and a two- year trail was conducted in Canada (Konstan, 2008; Lc & Stanojevic, 2007).

Targeted group of patient (age)	**Time**	**Previous condition**	**Observation**
84 children (from the age of 5-adult)	4 years	Mild lung disease with FEV1>60% predicted	Reduction in 89% of the annual rate of decline in FEV% predicted under the age of 13 years and no significant effect on adult
142 patient (from age of 6-18)	2 years	FEV1>60% predicted	Reduction in 49% of the annual rate of decline in (FEV% and FVC%) being predicted

*Abbreviations:FEV1:Forced Expiratory Volume in 1-second; FVC: Forced Vital Capacity (Lands & Dauletbaev, 2010)

From Table 4, these data provide an advantageous result, on the annual rate of decline of FEV1 % predicted in children with mild lung disease (Konstan, Byard, Hoppel, & Davis, 2002). From this data it's been also showed that high-dose of ibuprofen slower threat of progression in lung disease. regardless of these clinical effectiveness, ibuprofen has been used by few patients due to some adverse events like GIT toxicity, GIT bleeding, decrease esophageal motility (Mackey & Anbar, 2004) and high dose of ibuprofen causes acute severe nephrotoxicity while treating with IV aminoglycosides (Kovesi, Thomas, Swartz, & Noni, 1998; Lands & Dauletbaev, 2010; Lewis et al., 2008).

The clinical studies also support that high dose of administration of ibuprofen translates into a clinical benefit in animal models with chronic infection , this also recommended that high-dose ibuprofen may possibly decrease the inflammatory response without impairing bacterial clearance (Oermann, Sockrider, & Konstan, 1999). CF lung disease is characterized by a dysregulated neutrophilic inflammation.

Higher dose of ibuprofen is verified clinically to slowing down the development of lung disease in the treatment of cystic fibrosis, though concerns regarding prospective undesirable effects

have restricted the use of ibuprofen in the patients of CF. Thus for pulmonary administration it is possible to manufacture therapeutically steady dosage formulation along with extreme low doses and be capable to formulate and manufacture proficiently to overcome the restrictions of currently available dosage forms. Dose of inhalable formulation is (4 to 5) times less in the comparison of high dose of conventional oral therapy. Sheik at al. supported that, an inhalable formulation of ibuprofen, alone or in blend with any antibiotic, might hold the possibility to alter the beneficial approaches for CF, and can likewise decrease the weight of the treatment CF patients in long run (Sheikh, Pozzoli, Ong, Young, & Traini, 2017). Formulations of ibuprofen with capacity of a high drug loading & less included polymers been examined, and were characterized by an improved cellular uptake along with better mucus penetration (Al-Hallak, MHD, Sarfraz, Muhammad, Khan Azarmi, Roa, H Finlay, & Löbenberg, 2011). Ibuprofen in mixture with ciprofloxacin an antibiotic (combination therapy), and mannitol formulated by a co-spray drying technique evolved in suppressed local chronic infection, improved mucus clearance as well (Szabó-révész, 2018; Y. Yang, Tsifansky, Shin, Lin, & Yeo, 2010). Compositions of meloxicam in nano & micro size range with or without carrier have also been tried and may offer new choice of treatment in CF (Chvatal, Farkas, Balashazy, Szabo-Revesz, & Ambrus, 2017).

2.3 Use of Aspirin in the Treatment of Chronic Obstructive Pulmonary disease (COPD)

Chronic obstructive pulmonary disease (COPD) is one among the foremost common cause among the top ten causes of morbidity, mortality worldwide. Each year around $30 billion money is being estimated in the treatment of COPD patients in US. COPD, is a chronic inflammatory respiratory disease that is characterized by wheezy, shortness of breath, chest tightness, and coughing along with the mucus secretion (Diogo, 2018) . People having COPD, airways of lung may become partly blocked from swelling or mucus causing difficulties in

breathing. With these airways there are tiny sacs (like little balloons) use to inflate and deflate while breathe in and out but patient suffering with COPD these sacs like balloons become inflexible and due to chronic inflammation, it causes problems in breathing (Snell, 2019). Once the fundamental changes of COPD are irreversible, but individuals with COPD will alternately experience acute exacerbations during the events of lung infection. These events might be treated, but the pathology of underlining cause cannot be changed , from Figure 3 (Wayne,W. LaMorte, 2017).

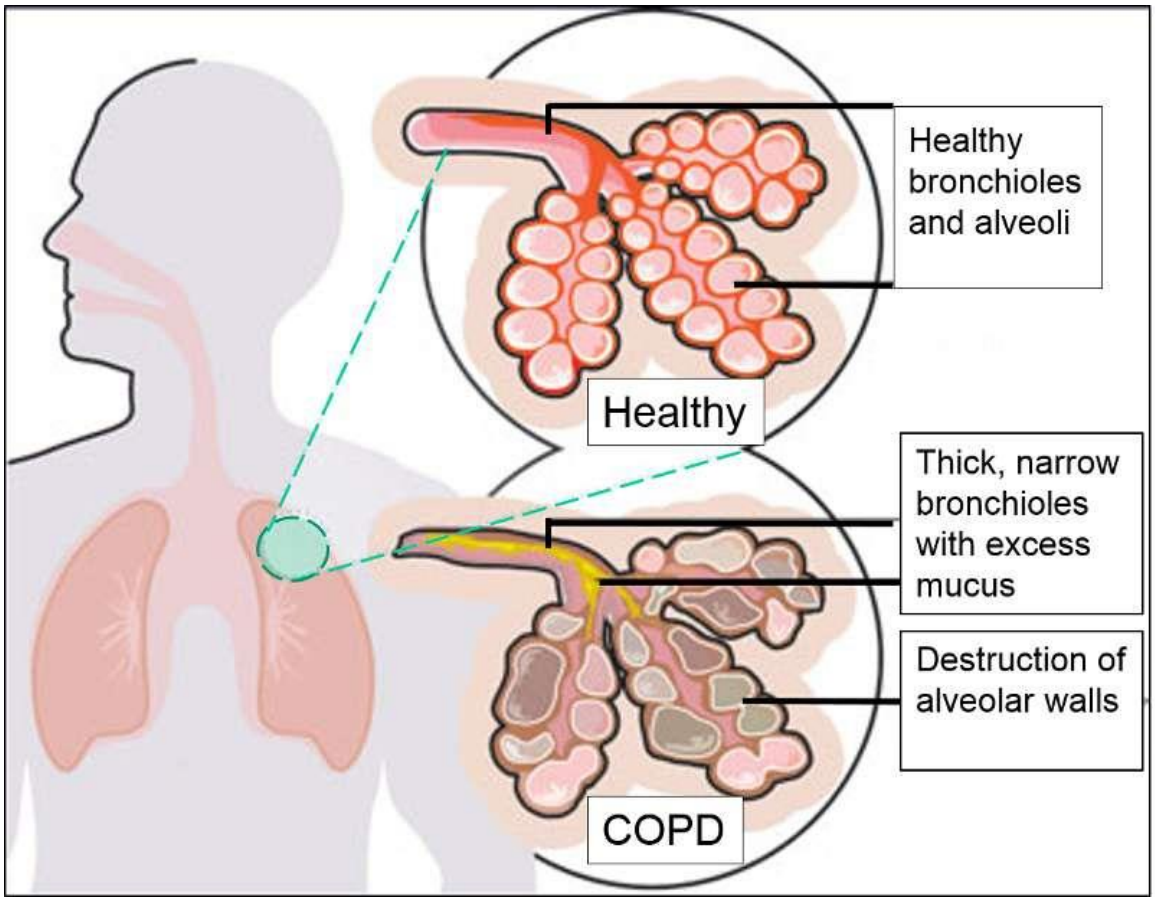

Figure 3: Comparative visualization of healthy lung and lung affected by Chronic Obstructive Pulmonary Disease (COPD) (Wayne,W. LaMorte, 2017).

Aspirin has many proven and well established therapeutic capabilities due to its effectiveness as an analgesic, an antiplatelet, an anti-inflammatory agent and an antipyretic while taken orally. Aspirin potentially gives therapeutic effect on chronic obstructive pulmonary disease

(COPD) patient (Harrison et al., 2014; Hermansson & Stro, 2013). Recent studies show that, anti-platelet drug such as aspirin which prevents blood clots as clots may get accumulated in blood vessels causing difficulties in oxygen generation among tissues thus, improves clinical condition in acute exacerbations in chronic obstructive pulmonary disease (AECOPD) patients. As aspirin worked as an analgesic, this is very effective as an anti-platelet drug, but little has been found concerning the impact of long term use of analgesic (aspirin) on acute severity of COPD (Diogo, 2018).

Table 5: According to researcher's investigation (hold at Massachusetts General Hospital) regarding prolong use of aspirin(orally) in patient with COPD (AECOPD) (Diogo, 2018).

Rate of hospital mortality	**Use of mechanical ventilation**	**Hospital length of stay (LOS)**
1.0% - aspirin users 1.4% - non users	1.7% - aspirin users 2.6% - non users	Intermediate of 3 days - aspirin users 4 days - non users

In table 5, the data was collected from 206,686 patients; there age was approximately ≥40 years suffering from hospitalized AECOPD. Here, long-term aspirin in oral dosage form users, mortality rates in hospital is lower than the nonusers (1.0% vs. 1.4%), also risk of invasive mechanical ventilation is lower (1.7% vs. 2.6%) and risk of non- invasive positive pressure ventilation (7.6% vs. 7.2%) was not different that much efficiently. LOS was noticed of being short in the user of aspirin than the nonusers (median of 3 days vs. 4 days). By using these data, it can be said that users of aspirin for a long time have lower rate of hospital mortality, lower use of invasive mechanical ventilation and also shorter LOS.

A study was conducted by lead researcher Dr. Ashraf Fawzy, among 1,700 patient with COPD and found that about 45% of patients were taking aspirin orally (a lower dose on regular basis) moreover, found more better quality of life and less shortness of breathing the patients who

took aspirin on regular basis at lower dose (81 mg) comparing with patients did not administrating aspirin (Steven, 2014).

Aspirin-acute severity association in COPD (Soyseth et al., 2011) requires more investigation and studies in terms of using aspirin for pulmonary disorders. Use of aspirin is not directly associated with the treatment of COPD patients but COPD patients might have history of cigarette smoking along with the risk of heart diseases like stroke or thrombosis. Aspirin helps to inhabit the formation of prostaglandins produced by COX, responsible for the transmission of pain session into the brain and thromboxane A_2 responsible for the aggregation of platelets providing anti- inflammatory and anti- platelet action. Thus mechanism of aspirin to prevent the inflammatory pathways and activated state of platelets shows potential benefit in other aspects for instance, ARDS, sepsis and cardiovascular diseases-related to death (Gando, 2010; Toner, McAuley, & Shyamsundar, 2015).

2.4 Use of NSAIDs in the Treatment of Lung Cancer

In US, lung cancer is one of the foremost cause of death (American Cancer Society, 2006) in men it causes approximately 951,000 deaths and in women approximately 427,000 deaths in 2008 (Ferlay et al., 2010; Jemal et al., 2011) however the courting is nearly 29% for all cancer mortality(American Cancer Society, 2006). Like other cancers lung cancer is also characterized by uncontrolled growth of cells (Hammerschmidt & Wirtz, 2009) of the lung tissue which later on can spread beyond the lung by metastasis into the other body parts (Bergman, 2017).

There are several different types of lung cancers, such as:

- Small cell lung cancer
- Non-small cell lung cancer

Among them NSCLC delocalized in character and SCLC localized in character, are the two main types of lung cancers.

Chronic inflammation has an important contribution in the progress of cancer (Brasky et al., 2012) and increase the risk of lung cancer and, thus there are some agents like NSAIDs that reduce chronic inflammation and reduce the risk of lung cancer (Marisa, David, & Randall, 2017).

NSCLC is the most frequently occurring lung cancer and adenocarcinoma (40%), large-cell carcinoma (9%), squamous-cell carcinoma (30%) these three are the sub types of NSCLC. NSAIDs provide anti-inflammatory effect by inhibiting prostaglandins through the suppression of COX-1 & COX-2 pathways by targeting the metabolic pathway of arachidonic acid. NSCLC over express COX-2 pathway (Hida et al., 1998; Mccormack et al., 2011) thus NSAIDs have effect in the reduction of COX-2 levels in the line of lung cancer cell (Hida et al., 1998). COX-2 is selectively over expressed in neoplastic tissue as well as inflammatory tissues of NSCLC. The development of malignancy is contributing through several mechanisms and COX-2 inhibitors represent efficacy potentially in case of originating apoptosis, prohibition of angiogenesis, decreasing invasiveness along with metastatic potential (Ramalingam & Belani, 2004; Szabo-revesz, 2018). Since the oral dose of NSAID is much higher than the required pulmonary effective dose thus, the inhaled dose of an appropriate NSAID should be considered and according to Tsubouchi et al. meloxicam can be a great choice to inhale, also has a great effect on lung cancer cell lines (A549 and PC14), and can be used as a combination therapeutic property in the treatment of NSCLC (Tsubouchiet al., 2000). The inhaled dose of Meloxicam is considered for the combination therapy of NSCLC and also celecoxib, rofecoxib have effective pulmonary effect and provide tolerable activity in the patients having NSCLC (in phase II study) (Evans & Kargman, 2004; Ishida et al., 2003). Regular use of NSAIDs like aspirin, reduces the colorectal cancer risk, gastrointestinal cancers however still the effect of

NSAIDs and aspirin on the expansion and progression on lung cancer is controversial may be due to the restricted effect of aspirin on COX 2 tumor (Chan, Ogino, & Fuchs, 2014).

As, SCLC does not express COX-2 as like as NSCLC, raising a question on the therapeutic properties and preventive action of NSAID being used use for tumor subtype use and the finding indicates the association of SCLC risk by histology.

Table 6: Association between 10- years non aspirin NSAIDs use(orally) and risk of small cell lung cancer in Vital cohort study(n= 75546) (Brasky et al., 2012).

NSAIDs	**Cases of SCLC (n= 111) n (%)**	**Non- cases (n= 75435) n (%)**	**Adjusted minimally HR (95% CL)[a]**	**Multivariable adjusted HR (95% CL)[b]**
Non aspirin NSAIDs[c]				
Non- user	71(70.30)	49748(68.97)	1.00(ref.)	1.00 (ref.)
Low (<4d/wk or<4y)	23(22.77)	17210(23.86)	0.98(0.59-1.64)	0.98(0.58-1.67)
High (≥4d/wk & ≥4y)	7(6.93)	5171(7.17)	1.04(0.47- 2.29)	0.98 (0.43-2.21)
			P trend= 0.97	P trend= 0.94

*Abbreviations: CI: confidence interval, HR: hazards ratio; a: adjusted for (age, pack-years, sex, pack years squared, smoking, and other NSAIDs use; b: adjusted for age, race, sex, education, pack-years, body mass index, pack years squared, history of lung cancer, chronic-obstructive pulmonary disease, osteoarthritis or chronic joint pain, ulcer, migraine, chronic headache, rheumatoid arthritis, coronary artery disease, and other NSAIDs uses; c: includes ibuprofen, COX-2 inhibitors, naproxen (Brasky et al., 2012).

From table 6, it has been found that SCLC risk was not related with the use of Non-aspirin NSAIDs. Elevated use of any NSAID was indicative to an increased SCLC risk (Brasky et al., 2012). Association between (NSAID) being used orally and the treatment of lung cancer has been investigated through several studies but findings remain ambiguous so more studies are required for the use of NSAIDs in case of lung cancer while administrating orally and even in inhalable dosage form.

Chapter 3

Adverse Effects

3.1 NSAIDs Causes Aspirin Sensitivity and Aspirin Exacerbated Respiratory Disease (AERD)

Asthma is one of the most common inflammatory diseases of lungs. Use of aspirin and NSAIDs, in respiratory tract disorder is a matter of clinical concern (Risser et al., 2009). Air go inside throughout our nose then going downward into our throat, airways, and finally into the lungs while breathing. Lung contains a lot of air passages that carries oxygen into bloodstream. Symptoms of asthma occur when the airways lining swell up and the muscles surrounded with get constricted, after that the airways get filled with mucus, which reduce the amount of air being passed through. This condition lead to an Asthma attack(Sullivan, 2018). Around 5% of people are highly sensitive to NSAIDs (aspirin) and induce (AERD or ASA triad) which can cause life threatening issue also can trigger symptoms of asthma or allergy(nasal congestion, runny nose, cough, wheezing, breathing problems, bronchospasm, tightness in your chest, skin rash, urtecaria, facial swelling, abdominal pains, shock) (Carter, 2017).

People with asthma will develop an asthma attack after taking aspirin. The attack may vary from mild to severe and sometimes can cause death (Jenkins, Costello, & Hodge, 2002). Aspirin sensitivity cause similar symptoms as allergic reactions. Approximately 5 out of 100 people with asthma having sensitivity to aspirin suffer in this way. Other 95 people out of 100 with asthma are susceptible to take aspirin and medications of this group without having any effect with asthma. Children suffering from asthma have aspirin sensitivity rarely compare to adult (Jenkins et al., 2002). Some patients with asthma having sensitivity to aspirin will have to suffer from nasal congestion and polyps in nose as well.

The specific reason behind experiencing aspirin sensitivity in few people is still not clear. It is reported that, the sensitivity is linked with chemical imbalance which causes the extreme leukotrienes production. Allergy cells of lungs in the airways releases excessive amount of leukotrienesin the bronchial tubes of patients having asthma and lead to bronchial spasm of muscles and swelling of the walls of these tubes. The reason, why some people with asthma produce large amounts of leukotrienes after taking aspirin is mysterious. People having sensitive to aspirin will be sensitive to other NSAIDs like naproxen, ibuprofen (Varghese & Lockey, 2008).

Table 7: The frequency of aspirin intolerance in various clinical condition while taken orally (Settipane, 1993).

Population with various condition	**Frequency of Aspirin intolerance (%)**
Asthma	4-19
Rhinitis	~1.4
Nasal polyps	14-23
Chronic Urticaria	23-28
Normal	~0.3

In Table 7, The frequency has been found lower When history alone is getting used for obtaining data, and frequencies are higher while aspirin challenge trial being used alone or along with the data attained y history (Settipane, 1993).

Aspirin-exacerbated respiratory disease (AERD) causes by aspirin and other NSAIDs induced respiratory reactions in practice with sinusitis, asthma and chronic rhinitis (Goto, 2018). During the third or fourth decade of life an adult patient having AERD may typically develop refractory chronic rhinitis (Fahrenholz, 2003). The clinical condition called, association of aspirin sensitivity (ASA), nasal polyposis and asthma was being first described by Widal, Abrami and Ler-moyez in the year of 1922 (Fahrenholz, 2003). In late 1960 Samter and Beers recognize the clinical syndrome, known as aspirin triad/ Samter's triad. After that the syndrome

has been referred as aspirin-induced asthma (AIA), aspirin-sensitive asthma, aspirin idio-syncrasy, aspirin disease, and most recently, (AERD) (Fahrenholz, 2003).

Table 8:A comparison of three types of challenge with Aspirin in AERD patients (Fahrenholz, 2003).

	ASA challenge (orally) 51 AERD patients	**ASA challenge (Inhaled) 35 AERD patents**	**ASA challenge (Nasal) 51 AERD patients**
Sensitivity	89%	77%	89%
Positive predictive value	(97- 100) %	(96- 100) %	97%

Here in Table 8, it shows the data of aspirin sensitivity in three different aspirin challenges and positive value in these challenge confirms the diagnosis of AERD in patient with compatible history (Fahrenholz, 2003).

Aspirin and other NSAIDs execrate the patient's respiratory mucosal inflammatory diseases. In little patience, once after developing AERD it stays for the rest of life. Some patients having aspirin induced asthma, cross sensitivity has been identified to doses of some other NSAIDs such as, 98% for ibuprofen , for naproxen this is 100%; and for diclofenac 93% (Jenkins et al., 2002).

Though aspirin is one of the most common NSAIDs with therapeutic effect, caution should be taken before taking aspirin those who have sensitivity with aspirin and allergic diseases like, chronic urticaria, nasal polyps, and steroid-dependent asthma.

3.2 Prolong use of NSAIDs Induce SCLC risk

We have already discussed a lot of things regarding the current status of using NSAIDs in terms of lung cancer treatment in the section of therapeutic effect. Though there are analysis data showing that taking aspirin on regular basis may cause reduction in lung cancer mortality (Casado-Arroyo, Lanas, & Brugada, 2016) specifically on NSCLC, Conflicting results being

found from individual trial data and also some data are found on the aspirin effects, in SCLC which is unnecessary (Jiang et al., 2015; Maddison, 2017; Oh, Myung, Park, Lee, & Kwon, 2011). Aspirin doesn't have tremendous effect on the survival in SCLC cases because of the low expression of COX- 2 unlike NSCLC. There are evidence (Maddison, 2017) that aspirin being used in the low dose have no significant progress in survival with tumor in patients with SCLC, that study was conducted among 313 patients and from them 71 patients were taken aspirin regularly for more than 2 years while diagnosed with tumor (Maddison, 2017) rather than the prolong use of NSAIDs (aspirin) induces SCLC risk among the women and smokers in (table 9) (Brasky et al., 2012).

As, we already know that SCLC does not express COX-2 as like as NSCLC, raising a question on the therapeutic properties and preventive action of NSAID being used use for tumor subtype (Hida et al., 1998). There are few studies being investigated on inducing SCLC risk associated with NSAIDs use and the finding indicates the association of SCLC risk by histology. Further finding provide signal of heterogeneity with the association within morphologies of lung cancer and aspirin.

Table 9: Association between 10 years use of NSAIDs (aspirin) and small cell lung cancer risk in Vital cohort (n= 75546) (Brasky et al., 2012).

NSAIDs	**Cases of SCLC (n= 111) n (%)**	**Non- cases (n= 75435) n (%)**	**Adjusted minimally HR (95% CL)[a]**	**Multivariable adjusted HR (95% CL)[b]**
Aspirin				
Non- user	38 (38.00)	37657 (53.94)	1.00 (ref.)	1.00 (ref.)
Low (<4d/wk or<4y)	22 (22.00)	16812 (24.08)	1.16 (0.66-2.04)	1.18 (0.66-2.09)
High (≥4d/wk & ≥4y)	40 (40.00)	15350 (21.99)	1.66 (1.01-2.72)	1.71 (0.01-2.87)
			P trend = 0.005	P trend= 0.05
Low dose Aspirin				
Non- user	66 (63.46)	50960 (71.36)	1.00 (ref.)	1.00 (ref.)
Low (<4d/wk or<4y)	17 (16.35)	11673 (16.35)	1.13 (0.63-2.02)	1.13 (0.63-2.04)
High (≥4d/wk & ≥4y)	21 (20.19)	8779 (12.29)	1.33 (0.78-2.29)	1.34 (0.77-2.32)
			P trend = 0.29	P trend = 0.29
Regular strength aspirin				
Non- user	67 (63.21)	55191 (75.40)	1.00 (ref.)	1.00 (ref.)
Low (<4d/wk or<4y)	15 (14.15)	9439 (12.90)	1.32 (0.71-2.45)	1.32 (0.71-2.44)
High (≥4d/wk & ≥4y)	24 (22.64)	8568 (11.71)	1.75 (1.05-2.92)	1.78 (1.05- 3.02)
			P trend = 0.03	P trend = 0.03

*Abbreviations: CI: confidence interval; HR: hazards ratio; a: adjusted for age, pack-years, sex, pack-years squared, smoking years, other NSAIDs uses. b: Adjusted for age, race, sex, education, pack-years, body mass index, pack years squared, history of lung cancer, chronic-obstructive pulmonary disease, osteoarthritis or chronic joint pain, ulcer, migraine, chronic headache, rheumatoid arthritis, coronary artery disease, and other NSAIDs uses (Brasky et al., 2012).

In Table 9, multivariable adjustment has been shown between NSAIDs use and risk of SCLC. In Table 9, this has been shown that comparing to the non-users, high users of aspirin on a regular basis having regular strength was linearly related with the SCLC risk.

Table 10: Association of 10 years use of regular strength aspirin &risk of small cell lung cancer in the Vita cohort study , stratified on sex and smoking status (n = 75546) (Brasky et al., 2012).

Regular-strength aspirin	**10-year Use Non-user**	**10-year Use Low (<4 d/wk or <4 y)**	**10-year Use High (≥4 d/wk and ≥4 y)**	**P-trend**
Males SCLC				
cases/non-cases	38/24,410	10/4777	15/5483	
HR (95% CI)[a]	1.00 (ref.)	1.23 (0.56-2.71)	1.40 (0.70-2.78)	0.32
Females SCLC				
cases/non-cases	29/3085	5/4662	9/30,781	
HR (95% CI)[a]	1.00 (ref.)	1.39 (0.51-3.80)	2.72 (1.18-6.25)	0.02
			P-interaction = 0.15	
Former smokers (≥10 y since quit) SCLC				
cases/non-cases HR	21/19,611	2/3543	5/3779	
(95% CI)[a]	1.00 (ref.)	0.65 (0.15-2.86)	1.43(0.50-4.12)	0.66
Current/recent smokers (<10 y since quit) SCLC				
cases/non-cases	41/7884	11/1503	17/1414	
HR (95% CI)[a]	1.00 (ref.)	1.53 (0.74-3.17)	2.11 (1.13-3.96)	0.02
			P-interaction = 0.15	

*Abbreviations: CI: confidence interval; HR: hazards ratio; a: used for age, education, body mass index, pack-years, sex, pack-years squared, coronary artery disease, smoking, history regarding lung cancer, osteoarthritis, chronic-obstructive pulmonary disease, ulcer, migraine, rheumatoid arthritis, coronary and other NSAIDs use.

In Table 10, findings are shown for the association among aspirin and SCLC stratified on sex and smoking condition. Risk of SCLC is non- significant among users of regularly high strength aspirin than non-users. Among women, a strong linear increase with the danger of SCLC has been found for regular-strength aspirin. Association has been found much stronger

within current or recent smokers at baseline comparative to non-users. Elevated uses of regular-strength aspirin doubling the risk of SCLC.

Here a, prospective study with broad assessments of NSAID use and history of smoking along with the data of 75,546 peoples (men and women), being investigated to find the involvement between the use of aspirin and SCLC, which results finding no support in order to prove the hypothesis that prolong NSAIDs use reduces the risk of SCLC whereas, use of regular-strength aspirin was related to high SCLC risk overall among female and smokers (current or recent) in particular. In addition this findings give indication of heterogeneity within the association in the morphologies of lung cancer and use of NSAIDs (aspirin) (Brasky et al., 2012). From all the data this can be stated that prolong administration of NSAIDs (aspirin) orally induces SCLC risk among the women and smokers.

3.3 NSAIDs Induce Risk of Pulmonary Embolism

Non-steroidal anti-inflammatory drugs are the OTC drug that are available without prescription and being used in a wide range for chronic and acute disorder by patients widely (Kearney et al., 2006; Mcgettigan & Henry, 2006; Rafi et al., 2011). Pulmonary embolism occurs due to blood clots which travel toward the lungs from the legs or different parts of the body blocking the flow of blood to the lung. Symptoms vary depending on the involvement of patient's, clot size, other underlying lung and heart disease.

There are several studies that show selective and non- selective NSAIDs both are related to an increase risk of heart diseases and death related to this. The mechanism behind the involvement of NSAIDs with cardiac disorder is not clear. Use of NSAIDs is related to associate enhanced risk of symptomatic PE and this association often be partially explained by several underlying medical conditions. NSAIDs like diclofenac, providing high COX-2 selectivity, is more associated with the cardiovascular risk. Though traditional NSAIDs use to block both isoforms

of COX, vary from their degree of selectivity. Prothrombotic state being induced by selective COX 2 inhibitor resulting the inhibition of inhibiting prostacyclin afterward inhibit platelet aggregation initiated by thromboxane along with other agonists, vasoconstriction, proliferation of vascular smooth muscle cell &interaction of leukocyte–endothelial cell (Bilora, Adamo, Pomerri, & Prandoni, 2015; Catella-lawson, Crofford, & Cox, 2001; Graff et al., 2007). After that thrombomodulin expression occurs by the stimulation of prostaglandin (Rabausch et al., 2015). Due to COX inhibition reduction in the synthesis of prostaglandin produce a prothrombotic effect. COX-1and COX-2 both are expressed in the veins and arteries. Even from a current study it is found that COX exposed in huge amounts in smooth muscle cells of the vein rather than in the cells of artery (Bishop-bailey, Pepper, Larkin, & Mitchell, 1998).This indicates that the effect of COX inhibition in the venous vasculature .

(Two to three) fold increased danger of venous thrombosis and PE is associated along with the use of NSAIDs (Huerta, Consuelo et al., 2015) particularly within the first 30 days of treatment, this risk is dependent to the dose and time (Staa, Rietbrock, Setakis, & Leufkens, 2008).

Table 11: Risk of pulmonary embolism related to use of non- steroidal anti-inflammatory drugs orally (Rafi et al., 2011).

NSAIDs	**Cases** **n = 4433(%)**	**Controls** **n= 16802(%)**	**Adjusted OR*** **(95%CI)**
No use	1547 (34.4)	7283 (43.3)	Reference
Past use	2944 (65.5)	8835 (52.6)	1.23 (1.14–1.34)
Current use	442 (9.8)	684 (4.1)	2.39 (2.06–2.77)
Duration of use			
1–30 days	255 (5.7)	252 (1.5)	4.77 (3.92–5.81)
31–365 days	139 (3.0)	332 (2.0)	1.83 (1.47–2.28)
>1 year	48 (1.1)	100 (0.6)	2.14 (1.48–3.09)
Number of NSAIDs			
1	428 (9.5)	671 (4.0)	2.01 (1.80–2.24)
≥1	14 (0.3)	13 (0.1)	2.78 (1.63–4.69)
Switching between NSAIDs			
Recent use of non-selective drugs and previous use of selective drugs	34 (0.77)	63 (0.37)	1.43 (0.91–2.24)
Current use of selective drugs and previous use of non-selective drugs	34 (0.77)	78 (0.46)	2.10 (0.23–19.3)
Current use of selective drugs without history of non-selective drugs	10 (0.23)	18 (0.11)	1.53 (1.08–2.18)

*Abbreviation CI: confidence interval; OR: odds ratio. *: adjusted for hospitalizations and use of anticoagulants≤90 days and ≥1 day prior to index date(Rafi et al., 2011).

Increase in risk was observed to be dependent on the time in this study, almost 20,000 individuals is shown in table 11. After the adjustment for malignancy, surgery and trauma, PE found to be associated with the current use of NSAIDs (OR 2.39, 95% CI 2.06–2.77). For Traditional NSAIDs, the risk was utmost as well as the in general risk for NSAIDs was upmost within the first 30 days of exposure (OR 4.77, 95%CI 3.92–5.81), compared with (<1 year; OR 1.83, 95% CI 1.47–2.28) or long-term use (>1 year; OR 2.14, 95% CI 1.48–3.09). NSAIDs users did not experience an increased risk of PE during the use of one type of NSAID throughout the study (OR 1.08, 95%CI 0.97–1.19) in the comparison with the users of more than one type of NSAID (OR 1.73, 95%CI 1.59–1.88).

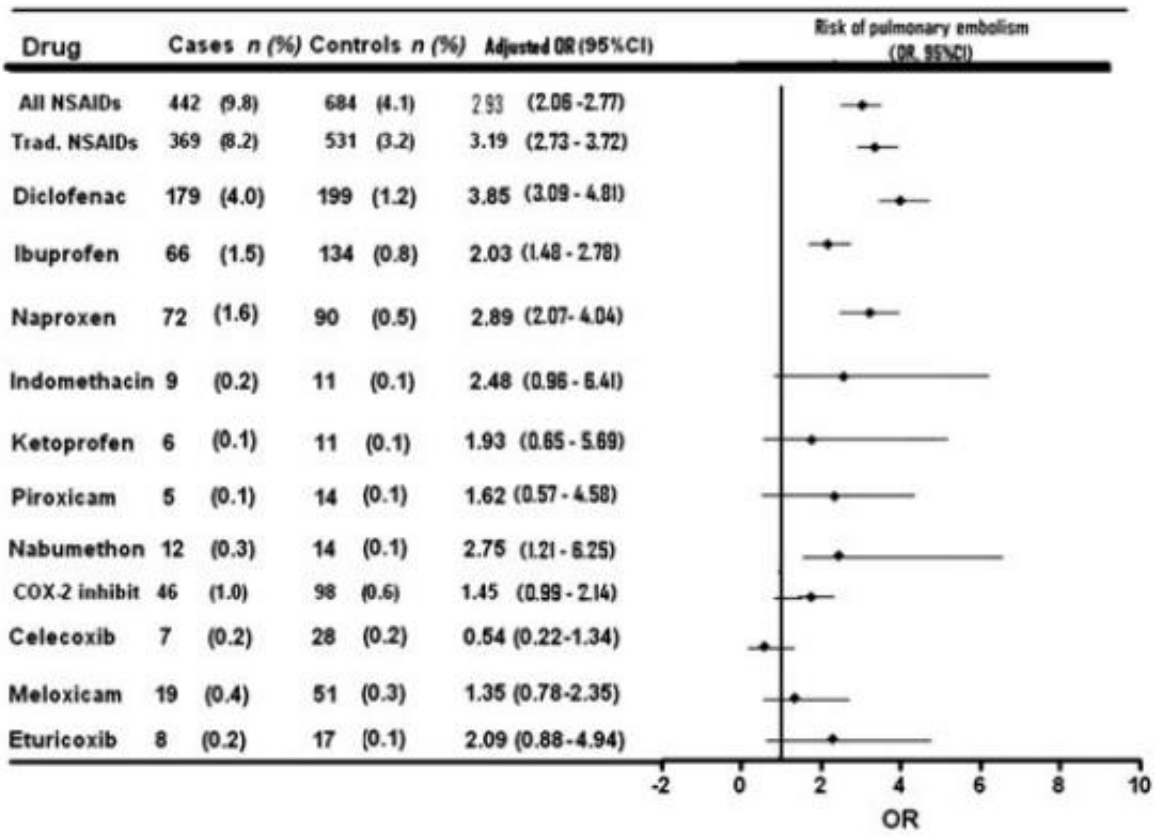

Figure 4: Diagram showing the risk of PE with current use of traditional and COX- 2 selective drugs through oral route of administration (Rafi et al., 2011).

From figure 5, it has been adjusted for hospitalizations and use of anticoagulants (≤90 days and ≥1) day prior to index date. CI, confidence interval; OR, odds ratio (Rafi et al., 2011).

Here in Figure 4, it is shown that traditional NSAIDs is highly associated with PE which is of threefold (adjusted OR 3.19, 95%CI 2.73–3.72). Risk of PE been increased by ibuprofen, diclofenac and naproxen increased the risk of PE, but the other NSAIDs were rarely being prescribed. The association PE risks and diclofenac has a dose- response relationship.

Finally, this can be said that, NSAIDs is association of NSAIDs follows a time- dependent risk pattern inducing risk of PE. Thus physician should be conscious regarding the higher risk of PE while prescribing these NSAIDs to the patients.

3.4 Association between NSAIDs Use and Community Acquired Pneumonia

NSAIDs abuse within the early stages of community-acquired pneumonia (CAP) has been currently related to a blunted presentation, course of preferential infection and greater risk of pleuropulmonary complications, especially pleural empyema (Messika et al., 2014; Voiriot, Guillaume et al., 2011).

Lower respiratory tract infections (LRTI) and CAP are the third foremost infectious reason of death (World Health Organization- WHO, 2018) and *Streptococcus pneumoniae* is the main cause behind this. NSAIDs are the most available OTC being used commonly by the patient also being prescribed mostly by general practitioners to reduce symptoms. According to a survey of French GPs' prescriptions it's been published that NSAIDs were prescribed by GPs in most of the patients with LRTI (Raherison et al., 2002) though this factor never appears in any guideline. NSAIDs may limit the inflammation and damage of the lung tissue (Esposito, 1984; Michie et al., 2010; Voiriot, Guillaume et al., 2011), but causing delay with antimicrobial therapy. By this manner use of NSAIDs predisposing to worse consequences thus alter the course of adults admitted into the hospital due to COP (Voiriot, Guillaume et al., 2011).

A study has been done to examine the effect of NSAIDs in pre-hospital treatment on the primary presentation and course of non-immune compromised adults who being referred to hospital for the purpose of pneumonia treatment. The study has been conducted within November 2002 to 2006 in the Tenon Hospital, and consisted 90 patients, 32 (36% of patients) had used NSAIDs in pre- hospital treatment, comparing to patients who were no exposed (young, had few comorbidities) having similarly sever disease during presentation. They had pleuropulmonary complications like pleural empyema and cavitation of lung (37.5% vs. 7%; P= .0009), and tentative to more invasive disease, with higher frequency of PE and bacteremia (25% vs. 5%, P= .014), specifically who have taken concomitant antibiotics (69% vs. 27%, P= .009). In spite of that, the patients with NSAID group had no serious dysfunction of organ and systemic inflammation. In multi-variable analyses, independent association between NSAID exposure and incidence of pleuropulmonary complications (OR, 8.1; 95% CI, 2.3-28) being found (Voiriot, Guillaume et al., 2011).

According to the findings of the study it can be said that NSAIDs may change the total course of infection and may result much serious complications. Also may increase the rate of hospital or admission in the ICU and also delay hospital course, specifically in patients who were not having antibiotics.

Finally, NSAID consumption or abuse at the primary stage of undiagnosed CAP shows potential danger to people who are young, active and healthy and lead to hospital administration even they can have organ failure. So, GPs have to be careful on the risks of prescribing NSAID without antibiotics and proper diagnosis in patients suffering from LRTI and CAP symptoms that leads to the risk of blunting common signs also causing delay in seeking medical care which continuously worsen the symptoms.

3.5 Use of NSAIDs in Pregnancy and Breastfeeding Women

High dose of NSAIDs are not safe in the pregnant or breastfeeding women having any kind of pulmonary disorders this can cause premature closure of ductus arteriosus along with pulmonary hypertension and many more in newborn (Risser et al., 2009). These effects are associated with indomethacin, naproxen, ketoprofen, and ibuprofen. During pregnancy pulmonary physiology gets altered compared to normal physiology. During this time the physiology and anatomy of cardiovascular and respiratory systems get changed. The upper respiratory tract and the mucosa of airway get changed due to hormonal change which produces hyperemia, mucosal edema, hyper secretion and increase in mucosal friability. With the expend uterus, diaphragm get displaced cephalad, diameter of thorax increases, chest wall get enlarged function of diaphragm stays normal (Madappa, 2018).

Use of NSAIDs are considered to be safe in pregnant and breastfeeding women in a low dose so, dose, duration and gestational period all these are potential factors during pregnancy and breast feeding period as a small trace amount of these medicines can be found in the breast milk. High dose of aspirin should be avoided during pregnancy and breast feeding women as high dose can cause intoxication or bleeding in the neonate but low dose of aspirin considers to be safe and cause no morbidity or mortality in neonate or newborn (Dionne & McCullagh, 1998; James, Brancazio, & Price, 2008; Monson, Kaufman, & Ross, 1976).

Chapter 4

Discussion

The findings from this review indicates a comparative study of Non-steroidal anti-inflammatory drugs (NSAIDs) being administered orally. NSAIDs are the most frequently used, prescribed and self-medicated group of medications among people of the whole world to manage the inflammation, fever and pain of different etiologies, but have risks associated with their use making them the second cause of some unwanted reaction, as this group of medication is getting exposed by a large population. However, a wide range of adverse reactions can be causes by NSAIDs which can be interpreted clinically in different manners.

The therapeutic effects are well established of NSAIDs in the large population in pulmonary disorders but adverse effect cause by NSAIDs are of great concern as, NSAIDs are being taken orally by all class of people throughout the world so, prescribing NSAIDs require careful consideration in patients with their individual risk factors. The data from this review indicates that, approximately 5% people are highly sensitive to aspirin along with other NSAIDs also associated with the risk factor of SCLC, AERD, pulmonary embolism, pleuropulmonary complications and other risk factors like symptoms of asthma or allergy (nasal congestion, runny nose, cough, wheezing, breathing problems, bronchospasm, tightness in your chest, skin rash, hives, facial swelling, abdominal pains, shock) these can be even life threatening. Use of all medication has its own therapeutic benefit and negative consequences as well. As using NSAIDs have many limitations associated with the treatment of various chronic diseases, the continuous development of targeted drug delivery systems is required and growing. The worldwide use of NSAIDs has meant that the adverse reaction of this group of drug is increasing commonly. Application of NSAIDs may also higher the risk associated with gastrointestinal problem, kidney disease and cardiovascular disease while being taken orally in the treatment of pulmonary disorder as the efficacy of the treatment highly depends on the drug

delivery technique and the drug concentration. So, to reduce adverse effect on the other organ, research is ongoing to make the delivery of drug directly targeted to the lung to achieve local and systemic treatment through pulmonary route of administration and for this the investigations and research are still going on but it requires more time. "Desensitization" is required in the management of AERD and other symptoms of aspirin and NSAIDs sensitivity in a better and successful manner. In the case of NSAIDs hypersensitivity, a huge number of compounds are belonging to NSAIDs group; only desensitization to aspirin has been adequately proved. Aspirin desensitization is a procedure with high-risk. Aspirin desensitization, a standard is being used to provoke the reaction, low aspirin dose (threshold dose) succeeded by increasing doses that are tolerated. In “silent desensitization” complete dose of aspirin (e.g., 600 mg) of tolerance state be induced, without provoking the primary reaction, followed by the time, sub-threshold and gradually administration of small dose. “Slow desensitization” and “rapid desensitization” are the other two protocols being used for patient’s desensitization with NSAIDs hypersensitivity. To reduce the negative impact of conventional treatment and for the innovation of the newly targeted nasal and pulmonary dosage form some parameters must be of better understand like, nature of therapeutic agents, cellular aspects, properties of delivery system, aerosol and techniques of pulmonary drug delivery, mechanism of pulmonary administration, deposition pattern of lung and type of devices that delivers drug etc. need to be carefully analyzed. Thus better and careful understanding of all these factors will help to establish maximum therapeutically efficient and beneficial inhaled or directly targeted therapy for pulmonary diseases of NSAIDs by minimizing negative impacts and analysis all the physiochemical and biological properties. As prolong use of NSAIDs have significant side effects there are a lot of challenges along with a great scope for the scientists and researchers to investigate and demonstrate all the parameters to achieve a targeted drug

delivery system for pulmonary route that could be safer and better approach with less negative impact of using NSAIDs in the treatment of pulmonary diseases.

Chapter 5

Conclusion and Future Prospects

This study suggested that the treatment using NSAIDs, is therapeutically appropriate as well as beneficial for some clinical conditions of pulmonary diseases and being used successfully by different types of patients among the whole population to treat a wide range of painful conditions. However the adverse reactions cause by NSAIDs cannot be overlooked and is a matter of great concern. Use of NSAIDs cannot be stopped permanently as more than 30 million of people using NSAIDs for different diseases regularly. Thus for the safer and more efficient therapeutic effect of NSAIDs approach of targeted pulmonary administration is the most possible solution for which, in near future to establish a successful targeted pulmonary r4oute of administration, things that should be considered are-

- Continuous research is must to ensure more efficient, effective, safer and better treatment opportunity.
- Researchers and pharmaceutical scientists should be more innovative regarding technologies and dosage form to reduce the clinical technical gaps.
- NSAIDs should be prescribes with more caution depending on the patient's intolerance.

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