# Manuscript Details

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**Abstract**

This review focuses on nasal and pulmonary delivery of NSAIDs (non-steroidal anti-inflammatory drugs) for fast-onset analgesia, for the potential prevention of Alzheimer's disease (AD), as well as for an add-on treatment in cystic fibrosis (CF) and non-small cell lung cancer (NSCLC). I discuss how the physicochemical properties of NSAIDs can be modified with respect to the biological characteristics of the target site. Innovative technology and/or dosage forms can promote an effective therapy.

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| **Keywords** | COX inhibitors; NSAIDs; physicochemical profiling; nose-to-blood; nose-to-brain; target to lung; nano drug delivery systems |

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P. Szabó-Révész

Modifying the physicochemical properties of NSAIDs for nasal and pulmonary administration

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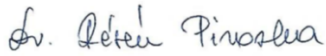

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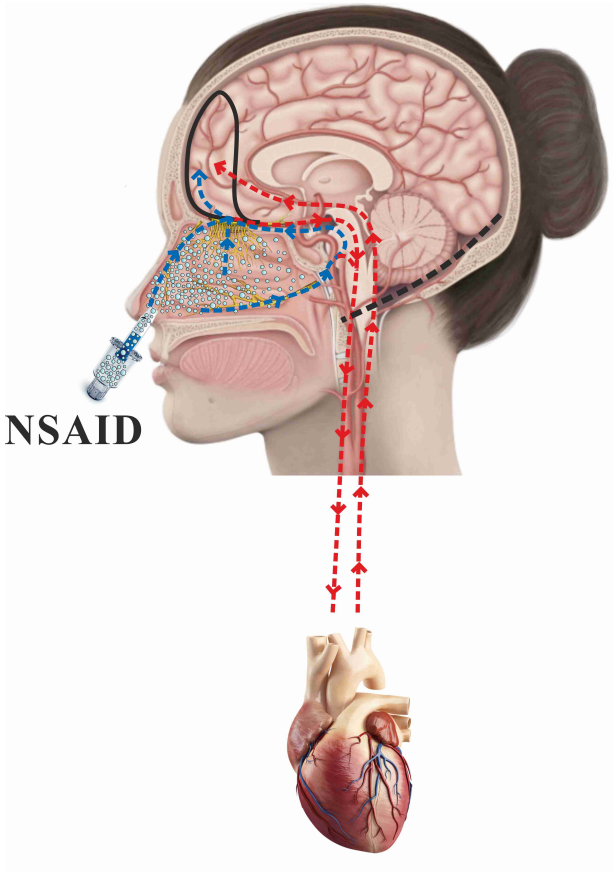
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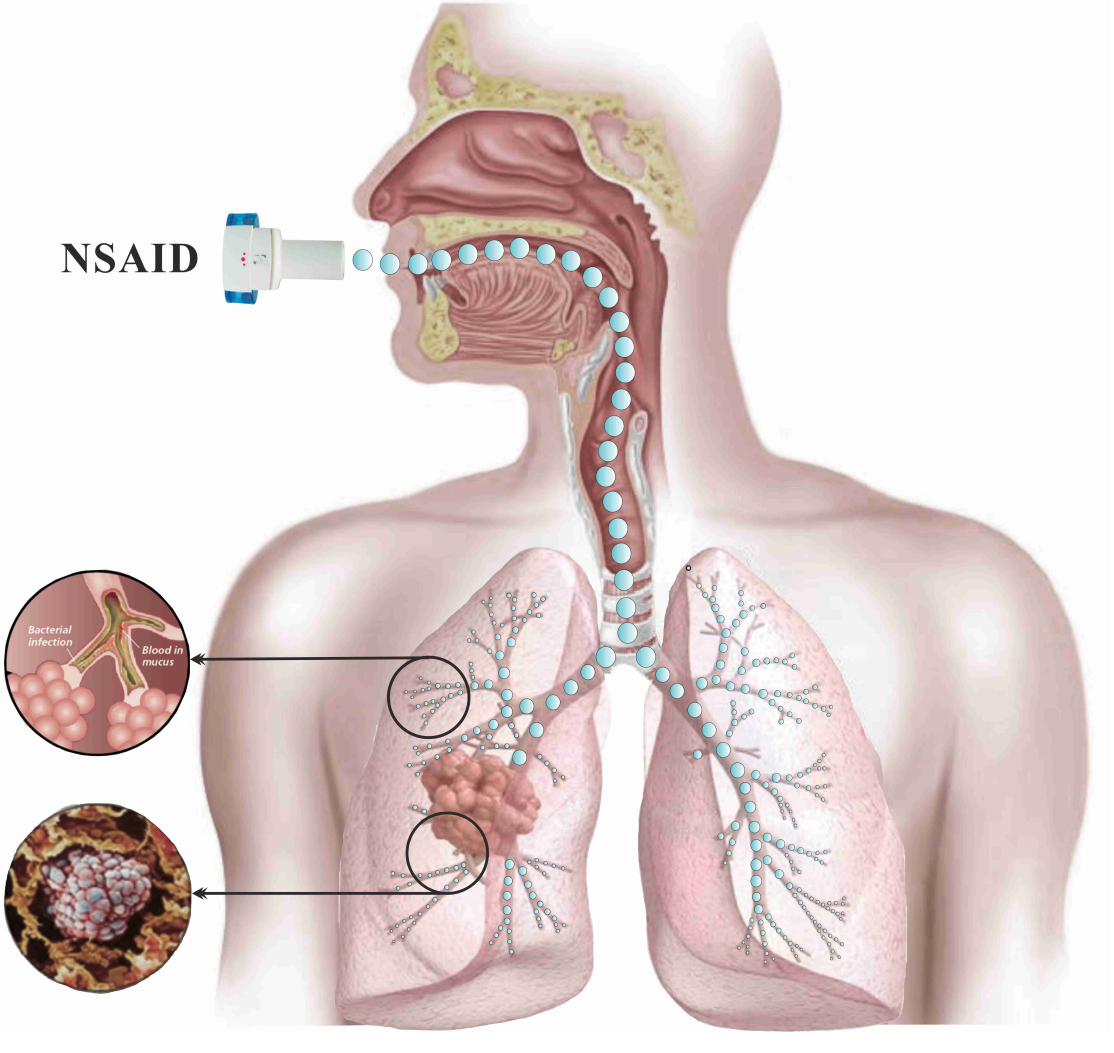
NSAID
Bacterial infection
Blood in mucus

# Modifying the physicochemical properties of NSAIDs for nasal and pulmonary administration

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**Abstract**

This review focuses on nasal and pulmonary delivery of NSAIDs (non-steroidal anti-inflammatory drugs) for fast-onset analgesia, for the potential prevention of Alzheimer's disease (AD), as well as for an add-on treatment in cystic fibrosis (CF) and non-small cell lung cancer (NSCLC). I discuss how the physicochemical properties of NSAIDs can be modified with respect to the biological characteristics of the target site. Innovative technology and/or dosage forms can promote an effective therapy.

Key words: COX inhibitors; NSAIDs; physicochemical profiling; nose-to-blood; nose-to-brain; target to lung; nano drug delivery systems

**NSAIDs in therapy**

The large family of NSAIDs are frequently used as analgesics, anti-inflammatory and antipyretic agents. Their biological effects are explained by the inhibition of the cyclooxygenase (COX) enzymes, which are responsible for the biosynthesis of prostaglandins that promote pain and inflammation. COX enzymes have 3 different isoforms: COX-1 is constitutively expressed in most healthy tissues, while COX-2 is an inducible form expressed in inflammatory cells in response to proinflammatory stimuli such as injury, bacterial endotoxins, tumor-promoting agent, etc. The newly discovered isoform COX-3 which is a variant of COX-1 is produced particularly in the brain [1]. Based on their selectivity, NSAIDs are (i) nonselective COX-1/COX-2 inhibitors, (ii) preferential COX-2 inhibitors with 5-50-fold selectivity and (iii) COX-2 inhibitors with >50-fold selectivity. NSAIDs are also classified according to their chemical structures and anti-inflammatory activities (Table 1) [2].

As shown is table 1 non-selective COX inhibitors include acetylsalicylic acid, indomethacin, aryl propionic acid derivatives, diclofenac, and naproxen. They have a long history as analgesics for acute or chronic pain (headache, migraine, menstrual, metastatic bone associated and postoperative pain, etc.), and also as antipyretics, as well as anti-inlammatory treatment for rheumatoid diseases. Nimesulide, meloxicam, and etodolac were the first NSAIDs with an enhanced safety profile, used as strong anti-inflammatory agents and later considered as preferential COX-2 inhibitors.

In fact, the COX-2 isoform was discovered in the early 1990s, and COX-2 inhibitors such as celecoxib, rofecoxib and etoricoxib possessing high selectivity and an increased inhibitory effect were approved. These agents were investigated in several inflammatory conditions such as non-rheumatoid inflammation, rheumatoid arthritis, osteoarthritis, spondylitis, add-on cancer treatment and prevention, and migraine [3]. Both COX-1 and COX-2 inhibitors are

tested in brain pathologies including Alzheimer's and Parkinson's disease, as well colorectal and breast cancers [4].

COX-1/COX-3 inhibitors may include paracetamol (acetaminophen), phenacetin and aminophenazone which are generally not considered NSAIDs because they have little anti-inflammatory activity. They reduce pain and fever, mostly in the central nervous system (CNS), and exert little effect in the rest of the body [1]

**Physicochemical profiles of NSAIDs**

Most of the NSAIDs are strong organic acids (carboxylic acids) with a dissociation constant (pKa) of 2–5 (but for some agents it may be □10) (Table 1). Their water solubility is pH-dependent, and in general it is poor or very poor. The acidic group is essential for the COX inhibitory activity.

NSAIDs differ in their lipophilic character wich is influenced by their aryl groups and additional lipophilic moieties and substituents. They are characterized by their □partition coefficient' which is a measure of how well the agent partitions between the lipid (oil) and water phases. Measured or calculated values are given in a database as logP (logarithm of octanol/water partition coefficient). When combined with pKa, it predicts the distribution of the compound in a biological system (logD, logarithm of octanol/water distribution coefficient e.g. at pH 7.4).

As NSAIDs basically have a lipophilic character, their permeability through membranes is „good" according to BCS (Biopharmaceutical Classification System) [5]. Most NSAIDs belong to Class II agents with low solubility and high permeability, and exhibit dissolution rate-limited absorption.

## Routes of administration

Worldwide, approximately 30 million people use NSAIDS daily. Tablets and capsules are popular dosage forms for oral administration, but are often associated with gastrointestinal side effects, mainly because of their acidic character [6, 7]. Other well-known routes of administration include injections, transdermal delivery systems and topical dosage forms. The poor solubility of NSAIDs gives grounds for different technological formulations to enhance their activity and reduce side-effects [8]. Nasal and pulmonary application are new approaches of significant therapeutic potential. However, based on the targeted biological environment, these routes of administration require the modification of the physicochemical characteristics of NSAIDs.

## Nasal application of NSAIDs

Intranasal administration is an effective way to deliver drugs into the systemic circulation as an alternative to the oral and parenteral routes for some therapeutic agents (Fig. 1 and Table 1). The nasal pathway may bypass the blood–brain barrier and allow centrally acting pharmacons to directly enter the CNS [9]. The main advantages of nasal administration include (i) a relatively large absorption surface, (ii) escaping first-pass elimination, (iii) a rapid onset of action, and (iv) non invasive and easy administration, offering improved compliance [8].

As NSAIDs are poorly dissolved at the nasal membrane (pH: 5.3-5.6), increasing their solubility and/or the rate of dissolution is a challenge to overcome in the development of nasal dosage forms, in order to enhance bioavailability (Table 1). Solubility may be improved by using salt forms, solubility-enhancing agents such as co-solvents (e.g. benzyl alcohol) or

complexing agents (e.g. cyclodextrins). The dissolution rate may be increased by particle size reduction to the micro- or nano range [10] or by breaking of crystal structure (amorphous form, applicable for a liquid or gel form containing the suspended active agent). Also, the residence time, i.e. the length of time the formulation spends in the nasal cavity should be lengthened by using mucoadhesive agents [11].

***Analgesia***

So far, the first and only intranasal NSAID product available in the market was approved by the US Food and Drug Administration in 2010 (Sprix$^{R}$, Regency Therapeutics, Shirley, NY, USA, current MAH: Egalet Corporation, Wayne, PA, USA). It contains the salt form of ketorolac (ketorolac tromethamine) and is indicated in adult patients for the short term (up to 5 days) management of moderate to moderately severe pain that requires analgesia at the opioid level The pivotal phase III study supporting its approval showed that patients required 34 percent less morphine within the first 24 hours following hysterectomy and hip replacement surgery compared to patients on on-demand postoperative morphine alone [12]. Currently, the results of a phase IV study comparing ketorolac tromethamine nasal spray with a sumatriptan nasal spray and placebo for the acute treatment of migraine, are under evaluation [13].

Based on literature data, meloxicam as a preferential selective COX-2 inhibitor could be a new candidate for nasal application to induce rapid-onset analgesia. For an enhanced nasal absorption, its salt form, meloxicam potassium monohydrate has been investigated [14]. Both *in vitro* and *in vivo* results indicate that this salt form is preferable for the development of an intranasal liquid dosage form. Besides, a nasal formulation of dissolved meloxicam, containing different solubility enhancers was patented by Castile et al. [15].

The solubility of meloxicam can be increased by over 270-fold, from 4.4 μg/mL to 1.2 mg/mL via nanonization (particle size □200 nm) and using solubilizing agents [16], resulting in a significant improvement of pharmacokinetic characteristics. *In vitro* and *in vivo* studies indicate that the longer residence time and the uniform distribution of nanonized meloxicam sprayed on the nasal mucosa result in better absorption and a higher AUC [17-19].

***Alzheimer's disease (AD)***

AD is a chronic neurodegenerative disease associated with a chronic neuroinflammatory environment in the brain [20, 21]. Observational epidemiological studies indicate that long-term oral administration of NSAIDs to patients having rheumatoid arthritis may reduce the risk and delay the onset of AD [22]. Therefore, NSAIDs might play a role in the prevention of AD. However, as only 1-2% of total NSAID plasma concentration reaches the brain, it is considered that intranasal administration would significantly increase the drug dose entering the brain [23, 24].

Experimental studies show that AD starts in the entorhinal cortex which is connected to the olfactory nerves, and spreads in an anatomically defined pattern [25]. Therefore, a nasal NSAID would readily reach the brain region where it is the most likely to be of therapeutic benefit [25].

Low-molecular-weight lipophilic drugs are fast absorbed into the brain via the intranasal route [26]. Parepally et al. [27] investigated the brain uptake of ibuprofen, flurbiprofen, and indomethacin. Flurbiprofen was found to be preferable to ibuprofen because of its 12.5-fold potency [28, 29]. Also, flurbiprofen inhibits both COX-1 and COX-2, thus it may be more effective than selective COX-2 inhibitors [30].

**Pulmonary application of NSAIDs**

Pulmonary application is a non-invasive method of drug delivery for systemic or local respiratory effects (Fig. 2). It usually allows for a reduction of drug dose compared to oral or parenteral adminstration. Inhalation delivery of NSAIDs can be especially useful for the treatment of cystic fibrosis (CF) and non-small cell lung cancer (NSCLC).

The main advantages of pulmonary administration include (i) the large surface of conducting airways of about 0.8 $m^2$, (ii) an effective local therapy, (iii) limited penetration into the systemic circulation resulting in less side effects, (iv) non-invasive, easy administration offering good compliance (Table 2).

The physicochemical properties of NSAIDs allow for pulmonary application as an aerosol, which is a two-phase system containing solid particles or liquid droplets dispersed in air or other gas phase. Solid particles may be administered in a dry powder inhaler (DPI) system, while liquid preparations contain the drug in a dissolved form. Both are suitable for NSAIDs as they are properly soluble at pH 7.4 of the lungs, offering a good therapeutic effect. NSAIDs are also ideal for inhalation because they have small molecule weight and a relatively high logP value [31].

To enhance the deposition and thus the bioavailability of NSAIDs from pulmonary formulations, we need to ensure (i) a controllable particle/droplet morphology (size, surface), (ii) a narrow interval in particle size distribution, (iii) low bulk density of solid particles, (iv) an ideal aerodynamical property of particles, (v) a high fine-particle fraction, a small mass median aerodynamic diameter and a high emitted dose, as well as (vi) long residence time provided by mucoadhesive agents [32] (Table 2). Different additives (surfactants, polymers, etc.) may also be used to produce drug delivery systems with a better and faster effect.

*Cystic fibrosis (CF)*

CF is a genetic disorder characterized by build up of thick, sticky mucus mostly in the lungs, but also in other organs (e.g. pacreas, liver, kidneys, intestine, etc). CF mucus contains less water, and mucins with a special cross-linked structure, resulting in high viscoelasticity. Ruge et al. reported that the pore size of CF mucus falls into the nano-size range. As pulmonary drug delivery requires permeation through the porous sticky mucus layer [33], inhalable nanostructured particles (□1000 nm) are the suitable choice for an effective penetration [34]. NSAIDs must be evenly distributed throughout the airways and the alveolar tissue that contain a wealth of inflammatory cells [35].

Different NSAIDs (ibuprofen, indomethacin, diclofenac sodium) have been investigated for inhalation [36]. So far, ibuprofen (per os) is the only NSAID approved for chronic use in CF, as it was found to slow the progression of lung disease in children [37]. In case of pulmonary delivery, its dose is four to five times less compared to conventional high dose oral therapy. Sheikh at al. reviewed the role of NSAIDs in CF treatment, and concluded that an inhalable form of ibuprofen, either alone or in combination with an antibiotic, could hold the potential to revolutionize the therapeutic approaches for CF, and may also reduce the treatment burden of the CF community in the long term [38]. Ibuprofen-containing formulations with a high drug loading capacity and less added polymers have been investigated, and were found to be characterized by an increased cellular uptake and enhanced mucus penetration [39]. Ibuprofen in combination with an antibiotic (ciprofloxacin) and mannitol formulated by a co-spray drying technique resulted in enhanced mucus clearance and suppressed local chronic infection [40]. Meloxicam-containing carrier-free and carrier-based compositions in the micro- and nano-size range have also been tested and may offer new treatment alternatives in CF [32].

### *Non-small cell lung cancer (NSCLC)*

NSCLC is the most common type of lung cancer. COX-2 is selectively overexpressed in neoplastic and inflammatory tissues. NSCLC overexpresses COX-2, which contributes to the progression of malignancy by several mechanisms which represents the basis for the potential efficacy of COX-2 inhibitors in terms of induction of apoptosis, inhibition of angiogenesis, and decreased invasiveness and metastatic potential [41]. Tsubouchi et al. evaluated the effects of meloxicam on lung cancer cells' proliferation, and concluded that meloxicam may be useful add-on therapeutic agent in the treatment of NSCLC [42].

In preclinical studies the COX-2 inhibitors celecoxib and rofecoxib, as well as meloxicam as a preferential COX-2 inhibitor were investigated to improve the efficacy of NSCLC therapy [43]. Compared with coxibs, meloxicam has reduced cardiovascular toxicity; however, its anti-tumor efficacy has not been proved in clinical settings. In a phase II study the combination of meloxicam, carboplatin, and docetaxel were tested in patients with advanced NSCLC. Meloxicam added to carboplatin plus docetaxel demonstrated acceptable tolerability with encouraging activity in advanced NSCLC patients. It should be noted, that patients received oral meloxicam (150 mg daily). Similarly, in another study the addition of meloxican (per os) was reported to enhance the reponse to paclitaxel/carboplatin in patients with advanced NSCLC [44]. As the oral dose is much higher than what would be required for an effective pulmonary effect, the inhaled dose should be considered for the combination therapy of NSCLC.

## Conclusion

The therapeutic effects of NSAIDs are determined by their physicochemical properties. Successful nasal application requires the increase of solubility by using the salt forms or using penetration enhancers. Also, micronization and nanonization of the active agent may increase the extent of dissolution for a fast onset of analgesia or to target the brain to potentially prevent the development of AD. In case of pulmonary application, modifying the physicochemical properties of NSAIDs is not enough alone, because the pathological lung condition requires special formulations to ensure a targeted anti-inflammatory effect in CF and NSCLC. Nasal and pulmonary administration of NSAIDs is promising, but further studies are needed to characterize their therapeutic efficiency and to optimize their formulations.

**Author declaration**

I wish to confirm that there are no known conflicts of interest associated with this publication.

**Acknowledgement**

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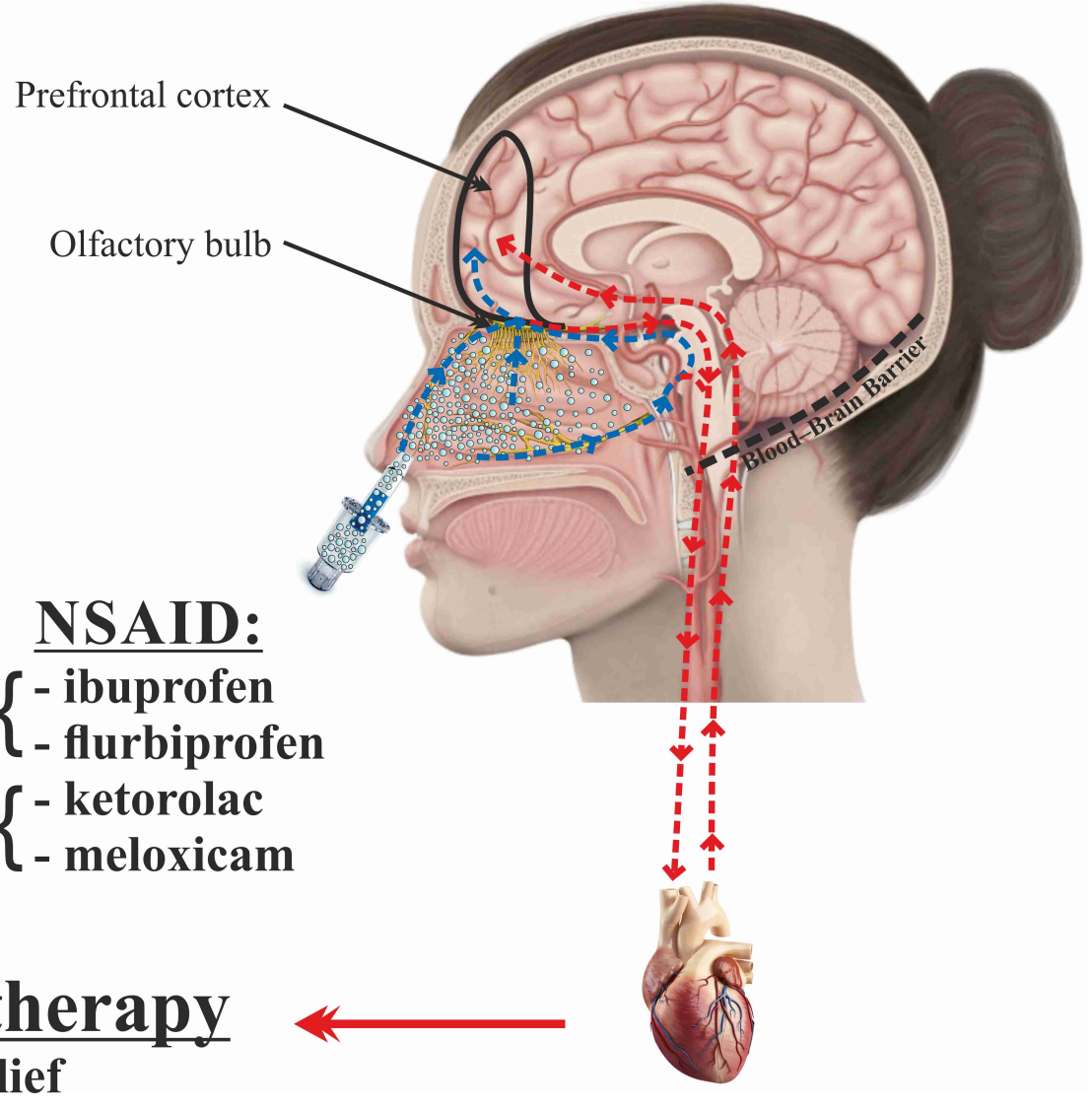
■:DIRECT WAY
■:INDIRECT WAY

# Brain therapy

## Alzheimer's disease



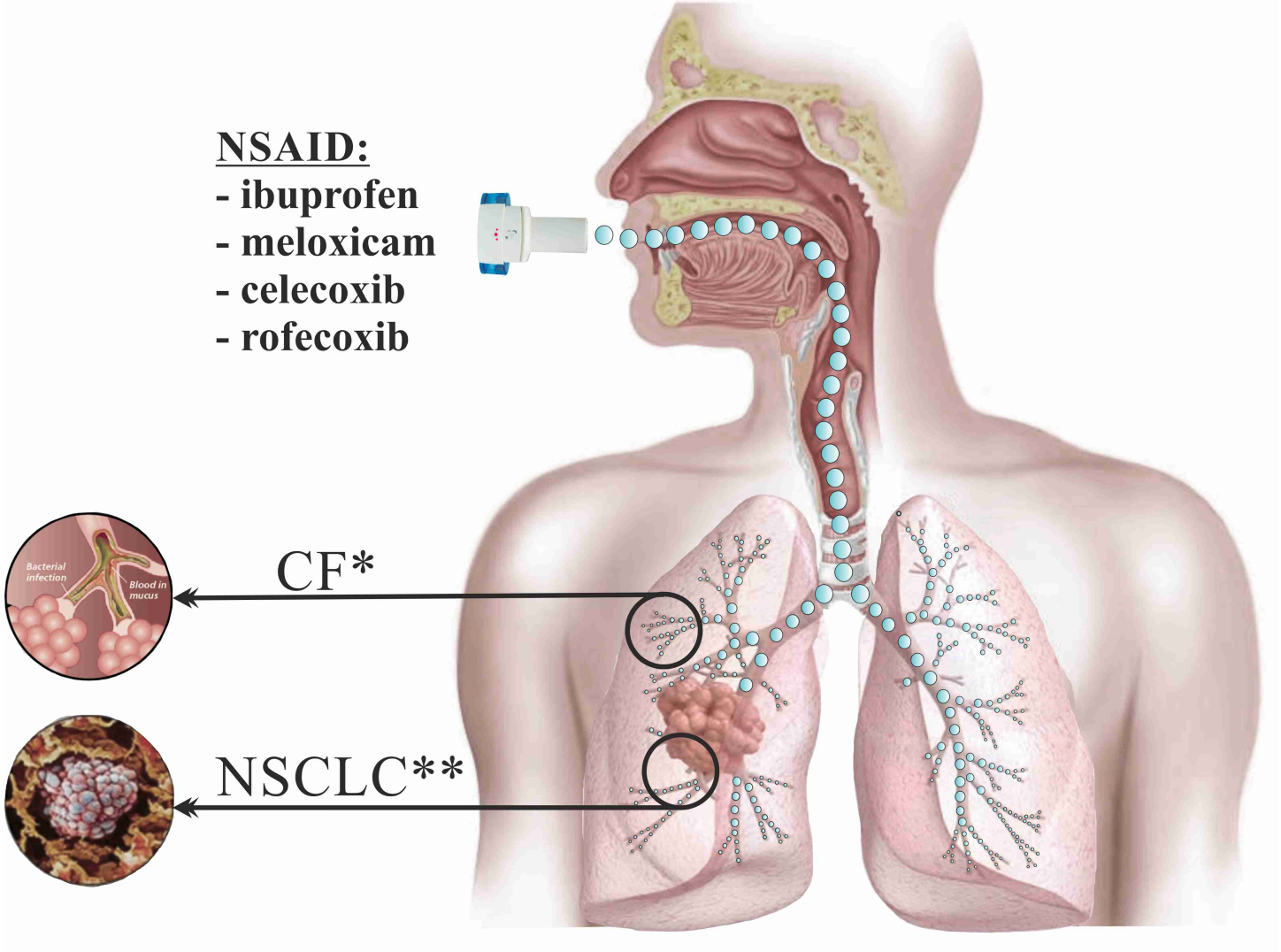

## NSAID:

Alzheimer { - ibuprofen
- flurbiprofen

Analgesia { - ketorolac
- meloxicam

# Systemic therapy

## Pain relief




# Local therapy

Patient / Disease-specific

Anatomical diameters, Drug deposition

* Cystic Fibrosis

** Non-Small Cell Lung Cancer

Figure captions

Figure 1 Nasal administration of NSAIDs to reach the blood and the brain

Figure 2 Figure 2 Pulmonary administration of NSAIDs for potential use in CF and NSCLC therapy

Table 1. Chemical classification and physicochemical characteristics of the most important NSAIDs *

| Derivative | Drug | Selectivity | pKa | logP | Solubility in water at 25 °C (mg/L) |
|---|---|---|---|---|---|
| *Salicylates* | Acetylsalicylic acid | [1]non-selective | 3.49 | 1.19 | 4600.0 |
| *Acetic acid derivates* | Indomethacin | [1]non-selective | 4.50 | 4.27 | 0.94 |
| | Diclofenac | [1]non-selective | 4.15 | 4.51 | 2.37 |
| | Aceclofenac | [1]non-selective | 3.44 | 2.17 | 2.00 |
| | Sulindac | [1]non-selective | 4.70 | 3.42 | 3000.0 |
| | Etodolac | [2]COX-2 preferential | 4.65 | 2.50 | 16.0 |
| | Ketorolac | [1]non-selective | 3.84 | 2.66 | 513.0 |
| *Oxicams/enol acid derivatives* | Piroxicam | [1]non-selective | 6.03 | 3.06 | 23.0 |
| | Tenoxicam | [1]non-selective | 2.21 | 1.90 | 14.1 |
| | Meloxicam | [2]COX-2 preferential | 4.08 | 3.43 | 7.15 |
| *Propionic acid derivatives* | Ibuprofen | [1]non-selective | 4.91 | 3.97 | 21.0 |
| | Flurbiprofen | [1]non-selective | 4.42 | 4.16 | 8.00 |
| | Ketoprofen | [1]non-selective | 4.45 | 3.12 | 51.00 |
| | Naproxen | [1]non-selective | 4.15 | 3.18 | 15.90 |
| *Fenamic acid derivatives* | Mefenamic acid | [1]non-selective | 4.20 | 5.12 | 20.00 |
| | Flufenamic acid | [1]non-selective | 3.88 | 5.25 | 9.09 |
| *Arylsulfonamide* | Nimesulid | [2]COX-2 preferential | 6.86 | 2.60 | 18.00 |
| *Coxibs* | Celecoxib | [3]COX-2 selective | 10.07 | 3.90 | 3.30 |
| | Rofecoxib | [3]COX-2 selective | 14.84 | 3.20 | 11.00 |
| | Etoricoxib | [3]COX-2 selective | 19.69 | 3.70 | 3.00 |
| *Anilids, Pyrazolone* | Paracetamol | COX-3 inhibitor | 9.38 | 0.46 | 4150.0 |
| | Phenacetin | COX-3 inhibitor | 14.98 | 1.58 | 766.0 |
| | Aminophenazon | COX-3 inhibitor | 5.00 | 1.0 | 25.50 |

[1]non-selective: COX-1/COX-2 inhibitor
[2]COX-2 preferential: drugs that inhibit COX-2 at lower concentrations than COX-1 (5-50-fold selectivity)
[3]COX-2 selective: drugs that inhibit COX-2 (but not COX-1) at label dose (> 50-fold selectivity)

*DrugBank (http://www.drugbank.ca/drugs)

Table 2. Biological factors to be considered with respect to the route administration, and related physicochemical properties of NSAIDs

| **Nasal therapy** | |
|---|---|
| Biological factors<br>-Healthy nose- | Physicochemical properties<br>-NSAIDs- |
| - Mucociliary clearence<br>- Permeability<br>- pH<br>- Absorption<br>- Membrane thickness and surface<br>- Barrier with tight junctions<br>- Enzime activity | - Solubility<br>- Dissolution rate<br>- logP<br>- pKa<br>- Particle-size distribution<br>- Products:<br>• Liquid form (use of salt form, solubilizing agent)<br>• Gel form (polymer based carrier system)<br>• Dry powder form (micro- and nanoparticles) |
| **Pulmonary therapy** | |
| Biological factors<br>- Unhealthy lung- | Physicochemical properties<br>-NSAIDs- |
| - Mucociliary clearence<br>- Permeability<br>- pH<br>- Enzime activity<br>- Rheological characteristic (mucus)<br>- Mucus thickness<br>- Lung development<br>- Bacterial colonization<br>- Cell types per lung region<br>- Cell growth | - Solubility<br>- Dissolution rate<br>- logP<br>- pKa<br>- Density<br>- Particle-size distribution<br>- Aerodynamical properties of particles<br>- Products:<br>• Liquid form (solution)<br>• Dry Powder Inhaler (DPI) (carrier-free and carrier-based form) |