Barriers to Oral and Inhaled Drug Delivery: A Review

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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 project titled "Barriers to Oral and Inhaled Drug Delivery: A Review" submitted by Farhana Kamal (18146078) of Spring, 2018 has been accepted as satisfactory in partial fulfilment of the requirement for the degree of Bachelor of Pharmacy on August 11, 2022.

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Ethics Statement

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

Abstract

Oral and pulmonary routes of drug administration are the two most common modes to deliver drugs to patients owing to their non-invasive nature. Among the two, the oral route is still the most preferred one due to a number of advantages such as ease of administration without requiring any assistance that offers enhanced patient compliance and cost-effectiveness. Several factors affect absorption orally delivered drugs including drug solubility, permeability across the mucosa, and stable position in the gastrointestinal tract environment. It is fundamental to understand the physicochemical, biochemical, metabolic and biological barriers which limit the overall bioavailability of therapeutic agents to address the problems associated with decreased oral absorption and bioavailability. Pulmonary route of drug administration holds the potential to overcome these problems of reduced absorption associated with oral drug delivery. However, pulmonary drug delivery is also negatively affected by mechanical, chemical, immunological barriers along with behavioral barriers linked with use of inhaler devices and poor patient adherence. To this end, the present review discusses the barriers associated with oral and pulmonary drug delivery, along with highlights of the advantages and disadvantages of both routes of drug administration with future perspectives.

Keywords: oral, pulmonary, drug, delivery, routes, barriers

Dedication

Dedicated to my supervisor, Dr. Zara Sheikh

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All praise belongs to Allah (Subhanahu wa Ta'ala). He is the only helper; without His help it would be impossible for me to come this far. I would like to start by thanking and conveying my gratitude to my supervisor, Dr. Zara Sheikh, Assistant Professor of the Department of Pharmacy, Brac University. Without her consistent support and guidance, completion of my project would never be possible. For her consistent supervision, I shall always remain grateful towards her.

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List of Acronyms

IV	Intravenous
IM	Intramuscular
DDI	Drug-Drug interaction
GIT	Gastrointestinal tract
pMDI	pressurized metered dose inhaler
DPI	Dry powder inhaler
MDI	Metered dose delivery
CFTR	Cystic fibrosis transmembrane conductance regulator
CF	Cystic fibrosis
MSSA	Methicillin-sensitive Staphylococcus aureus
MRSA	Methicillin-resistant Staphylococcus aureus
TB	Tuberculosis
COPD	Chronic Obstructive Pulmonary Disease

Chapter 1

Introduction:

1.1 Background:

Therapeutic agents can be delivered to patients by various routes of drug administration, including oral route that is via the mouth or by the pulmonary route via inhalation to be delivered to the lungs (Vinarov et al., 2021). Both the oral and the pulmonary routes of drug administration are commonly used modes of delivering drugs to patients, although the oral route is most widely used. The oral route is the most familiar method of drug administration due to its non-invasive, cheap and easily accessible for the patients making this route more patient compliant, yet it is associated with numerous disadvantages such as decreased bioavailability owing to first pass effect, thus reducing the quantity of drug that reaches the systemic circulation (Homayun et al., 2019). On the other hand, pulmonary route can overcome the problems of oral drug delivery, however it associated with a number of barriers and formulation and device management challenges. (Agrahari & Mitra, 2016)

1.2 Objectives of the Review:

The objectives of the review are-

- to provide an overview of the oral and inhaled drug delivery systems
- discuss the barriers associated with oral and inhaled drug delivery
- summarise the pros and cons of both oral and inhaled modes of drug administration with future perspectives.

Chapter 2

Treatment via the Oral Route

2.1 Oral drug delivery system

Oral delivery (via swallowing through the mouth) is the most frequently accepted method of drug administration. For patients who can take and tolerate oral forms of medications, oral medications are convenient for them. Due to unique advantages of oral drug delivery specifically sustained and controlled release delivery, ease of administration, scope for large-scale development of solid formulations, patient accessibility, large surface area for absorption, oral delivery system has gained the most attention (Alqahtani et al., 2021).

About 60 percent of commercially available small molecule products are administered through oral route. According to a recent estimation, oral formulations show approximately 90 percent of the market share of all pharmaceutical formulations worldwide. Orally administered pharmaceuticals make up about 84 percent of the top-selling medications, which are growing at a 10 percent yearly rate (Prasad et al., 2017). Patient compliance with orally taken medications is higher than other routes of administration, specifically the parenteral routes namely intravenous, subcutaneous, and intramuscular modes of drug administration. Oral route is particularly advantageous to cure certain pathological conditions including cancers in the stomach and colorectal region, gastro-duodenal ulcers and gastroesophageal reflux disorder, inflammatory disorders and infectious diseases along with bowel diseases. These conditions can be treated by orally administered drugs by targeting the medication to some specific regions within the gastrointestinal tract (Ingersoll and Cohen, 2008).

Despite these benefits, developing oral formulations is challenging due to the physicochemical characteristics of medicines as most therapeutic agents are poorly soluble, subsequently

resulting in lower permeability. Additionally, absorption of drugs is hindered by poor chemical and biological stability along with the physiological barriers which may be pH-related, pumping by the efflux transporters and first pass metabolism by enzymes present in the gastrointestinal tract (Rubbens et al., 2018). Therefore, a detailed physicochemical characteristic understanding, biological barriers, GI permeability, pharmacokinetics, and pharmacodynamics of medications is important and required to develop oral drug delivery systems.

Furthermore, orally administered drugs undergo first pass effect which reduces the bioavailability. Liver is the major site for metabolism of a drug when administered orally. Other sites are gastrointestinal flora, mucosa, blood, limb etc. When the drug is administered it is metabolised by liver enzymes known as first-pass metabolism that results in a lower concentration of the active ingredient that get into the systemic circulation, thus reducing the therapeutic efficacy of the drug.(Alqahtani et al., 2021). This is the main drawback of oral drug delivery and for this reason oral medications are not suitable for emergency situations as it will take a much longer time for the drug to elicit a therapeutic response. (Pond & Tozer, 1984).

2.2 Barriers to Oral Drug Delivery

2.2.1 Biological Barrier

Drugs that administered by the oral route are mainly absorbed in the upper parts of gastrointestinal tract (small intestine). As the surface area and mucus thickness is less compared to the small intestine, therefore the absorption capacity of the stomach is relatively less compared to the small intestine (duodenum and jejunum). One obstacle of drug absorption in the gastrointestinal environment is the epithelial lining of the intestines. Epithelial cells lining the epithelium of the gastrointestinal tract are connected by the tight junction proteins named

zona occludens or junctional complexes which exist at the apical surface of the single-column layer of epithelial cells. Small, hydrophilic molecules usually pass through these gaps in between the cells supported by tight junction proteins and this route of transport is known as paracellular route. In order to create villi that contain microvilli, the epithelium on the apical surface projects with the lamina propria. Tiny projections protruding from the small intestine known as microvilli not only allow drug absorption in an enormous surface area (Zhuu et al., 2017) but also act as an enzymatic barrier to prevent the drug from breaking down by digestive enzymes present at the boundary of the epithelial layer of the intestine (Zupanci and Bernkop-Schnürch, 2017). Drugs have to pass through multiple layers of the gastrointestinal tract and encounter gastric juice and cross the pericellular matrix and thick layer of mucus which help to absorbed from the lumen of the GI tract (Vasir et al., 2003).

One more factor that effects drug absorption is the pH. Stomach pH changes in the state of fasting. The median basal pH for adult males is 2.18 ± 0.18 (Goldschmiedt et al., 1991). Hence, formulation considerations must be taken into account for drugs with less stability in order to protect such drugs from the harsh acidic environment of the stomach.

Pepsin is crucial for breaking down the majority of ingested proteins. During formulation of drugs that may be subjected to degradation within the stomach, it must be kept in mind that pepsin although active at an acidic pH becomes inactive at a pH of above 4 and hence this property could be utilized with the use of buffer in the formulation of drugs susceptible to degradation in an acidic environment. (Rouge et al., 1996). This could be achieved by the judicious use of enteric polymer coatings namely acetate phthalate and methacrylate-based polymers for shielding medications from degradation by the stomach's acidic pH conditions (Chen et al., 2000).

The development of an oral dose form must take the GI transit time into consideration. The time it takes for medication dosage forms to pass by the small intestine in humans is constant and is generally regarded to be 3 hours. It is also not affected by the physical properties of the dosage forms, for example density and size, also by meals (Dressman and Reppas, 2016). The bioavailability of the medicine is known to fluctuate along with the stomach transit time. This variation could ultimately result in erratic plasma medication levels, which would significantly reduce therapeutic efficacy. Propulsive and mixed gastrointestinal movements are the two important factors greatly affected by the fed or fasting state and also by the sleep cycle. Following oral administration, a drug's residence period is mostly determined by the peristalsis motilities, which determine the passing rate (Rouge et al., 1996). In the upper portions of the intestinal system, the transit rate is much higher, and it decreases toward the ileum. A medication capsule must travel the complete length of the small intestine in 3–4 hours. The amount of ingested fiber determines the length of the transit time, which is significantly longer in the large intestine. The duration of time a drug spends in the intestine mimics the absorption of both pharmacological preparations that prolong the release of the drug as well as medications that are slightly or slowly soluble in intestinal fluids. The transit or residence time is fundamental factors for small drug molecules as these medications transported by the carrier systems and are effectively absorbed in regions with such carrier systems (Dressman and Reppas, 2016). For example, majority of vitamin B2 is absorbed in the proximal small intestine by sodium-dependent, carrier-mediated transport (Said and Mohammed, 2006). Thus, factors that have an impact on intestinal motility could also have a profound impact on the amount of vitamin B2 reaching the systemic circulation. Overall, it is well-known that the duration of the GI residence time directly influences the amount of medication absorption following oral administration. (Sakr, 1999).

According to Custodio et al. (2008), food can decrease, enhance, postpone, or accelerate the absorption of medicines. Food has an impact on GI processes like emptying of drug into the stomach, intestinal residence time, secretion of bile acid as well as changes related to gastric pH and increased blood flow to the liver. Additionally, it may change the solubility of a particular drug that may further change drug permeability across the intestine due to changes in size, therefore changing the rate of dissolution and absorption. In general, co-administered food has a significant influence on hydrophobic medications or pharmaceuticals whose solubility is pH-dependent (Cheng and Wong, 2020). It is well established that high-fat meals raise pancreozymin (cholecystokinin) concentrations, which in turn induce bile secretion from the gallbladder within the GI system. In this context, solubilizing micellar carriers could provide a solution to enhance the solubility of these drugs that increasing the absorption of these slightly soluble drugs from the lumen of GIT (Shneider, 2001).

Some fruit juices are familiar to change how medications are transported and metabolized or increase how much of a drug is absorbed (Ameer and Weintraub, 1997). Although research has been done on the benefits of various juices like orange, tangerine, lime, and apple, grapefruit juice has received the most attention. According to theories on drug metabolism, these juices' ability to block drug transport and metabolism is due to their inhibition of the cytochrome P450 3A4 (CYP3A4) enzyme. Additionally, some elements in some of these juices, like flavonoids and furanocoumarins, block organic anion transporters and P-glycoprotein (P-gp) (Guo et al., 2000). Drugs may traverse the mucous membranes of GI organs like the mouth, jejunum, ileum, stomach, duodenum, and colon as they move along the GI tract.

The GI tract's mucosal barrier can be crossed by drug molecules in solution using a number of different processes, such as passive diffusion or active drug transport. Two distinct pathways are involved in passive diffusion: the paracellular pathway, in which the small, hydrophilic molecules pass through the gaps in between the cells through the tight junctions, and the

transcellular pathway, in which lipophilic drugs traverses over the cell membrane of the intestinal cells. Cell membrane transporters enable active drug transport, which is further subdivided into active inflow of drug and efflux pump. The physicochemical properties of drug compounds and their affinity for various transporter proteins define the relevance of each mechanism (Mannhold et al., 2009; Dahlgren and Lennernäs, 2019). Transcellular absorption is the primary route of absorption for small molecules. The pace of absorption is primarily influenced by the rate of drug transport across the membrane of the intestine, which is further determined by the physico-chemical properties of a drug. Overall, the absorption via the transcellular route is primarily caused by diffusion down a concentration gradient. Nonionized lipophilic medications having molecular weights more than 300 g/mol are usually absorbed by the transcellular pathway. (Lipinski, 2000; Avdeef, 2001). Drug molecules with molecular weights under 200 g/mol are absorbed via paracellular transport via tight junctions (Hayashi et al., 1997). Additionally, cationic molecules pass through the junctional complex of the intestinal epithelium more easily because of its overall negative charge (DiMarco et al., 2017). However, absorption by this channel is often minimal since most drug molecules cannot traverse the intestinal membrane freely due to tight junctions between cells with pore diameters of 4 to 8 nm. Additionally, the paracellular transport accounts for only 0.1-0.01 percent of the intestinal membrane's total surface area and becomes less accessible as one moves from the jejunum to the colon, leaving only a small window for drug absorption (Sugano et al., 2002).

Medication molecules must bind with a protein carrier, typically present in the apical membrane of the intestinal cells for a drug to be transported via carrier-mediated transport as opposed to passive diffusion. The apical and basolateral membranes of the GI tract express a number of transporters that are members of the ABC transporters superfamily and solute carrier (SLC) transporters for the inflow or efflux of endogenous compounds and xenobiotics. The process of absorption via this pathway activates energy and necessitates the breakdown of ATP

that occurs against a gradient of drug concentration, or from an area of lower drug concentration to one of greater concentration. Even though enterocytes show a variety of transporters, only a small subset of these transporters are known to be crucial in the intestinal absorption of medicines (Müller et al., 2017).

2.2.2 Physicochemical Barrier

Drugs must be released from their dosage forms, must dissolve in the GI fluid to be absorbed and elicit a therapeutic response. Therefore, the Biopharmaceutical Classification System (BCS; Table 1)'s classification of medications into four groups is based on two criteria: aqueous solubility and permeability (Amidon et al., 1995).

Table 1: The Biopharmaceutics Classification System.

Class I	**Class II**
High solubility	Low solubility
High permeability	High permeability
Class III	**Class IV**
High solubility	Low solubility
Low permeability	Low permeability

Permeability depends drug factors including polarity, charge, and lipophilicity (Lennernäs, 2007). If 90% of the prescribed dose is absorbed, a medication is considered to be extremely permeable. Drugs in BCS Class I are excellent candidates for oral administration because they have high solubility and permeability. On the other hand, because of their low solubility (BCS Class II), low permeability (BCS Class III), or both, some BCS classes present difficult oral delivery prospects (BCS Class IV). BCS Class II medications' capacity for oral absorption can be enhanced by speeding up their disintegration rate.

Drug metabolism can affect the oral bioavailability in addition to their solubility and permeability. The Biopharmaceutics Drug Disposition Classification System (BDDCS) was so

proposed by Wu and Benet (Wu and Benet, 2005). The BDDCS offers insights on how diet affects drug absorption as well as details on how drug absorption, elimination, and transport interact. As per the BDDCS, the primary route of elimination affects drug permeability. Drug interactions with transporters are not anticipated to be substantial for Class 1 BDDCS medicines because of their high solubility and extensive metabolism. Thus, the degree of the bioavailability of such medications shouldn't be significantly impacted by high-fat meals. But high-fat meals postpone stomach emptying, decrease absorption (Custodio et al., 2008). Due to their insolubility, Class 2 BDDCS medicines, that are less soluble and highly metabolized, may experience considerable transporter effects, primarily efflux transporter effects. As a result of the intestinal suppression of efflux pumps such P-gp transporters, high-fat diets may boost their bioavailability. A decrease or elimination of the impact of high-fat meals and a largely minimization of other drug transporter interactions may result from dosage form modifications that greatly improve the solubility of BDDCS class 2 medications. Due to their low permeability, Class 3 BDDCS medicines are thought to particularly susceptible to the effects of uptake transporters. Because fatty diets block intestinal uptake transporters, they can decrease the bioavailability of many medications. The main effect, however, will rely on the level of transporter inhibition as well as the substrate's relative affinity for the transporters if a medication is a substrate for transporters (influx or efflux). This may have no impact or unexpectedly improve the drug's bioavailability (Dressman and Reppas, 2016).

2.2.3 Metabolic and Biochemical Barriers

Pancreatic digestive enzymes (namely lipases, amylase, and peptidases) as well as intestinal enzymes primarily present in the lower GI tract are responsible for intestinal metabolism to occur. First-pass metabolism usually occurs at the brush border of the small intestine as a result of the action of these digestive enzymes (Barthe et al., 1999). Intracellular metabolism usually requires phase-I metabolizing enzymes like cytochrome P450 enzymes like CYP3A4 as well

as several phase-II conjugating enzymes involved in reactions like sulfation and glucuronidation, as well as other enzymes like esterase (Gibson and Skett, 2001). The distribution of ester-type pro-drugs like aspirin can occur primarily at the intestinal epithelium, despite the fact that it is a site for pre-absorptive metabolism (Thummel et al., 1997). The primary metabolic barrier, additionally the intestinal epithelium, is the hepatic first-pass metabolism. Membrane transporters can be divided into two groups: uptake transporters and efflux transporters. They help move medicines and endogenous substances into or out of cells. As a result, membrane transporters have a significant role in determining the bioavailability, disposal, and absorption of oral drugs (Shugarts and Benet, 2009). Solute carrier (SLC) superfamily members are the primary uptake transporters that allow xenobiotic medicines to enter cells, whereas ABC superfamily members are the efflux transporters (Giacomini et al., 2010). Efflux transporters, such as the bile salt export pump (BSEP), Pgp, MRP1-6, and BCRP, are highly expressed in the liver and gut that may pump out the drugs resulting in reduced absorption and consequently decreased therapeutic efficacy. P-gp is mostly found in the brush border surface of enterocytes in the small intestine and a major portion of the colon, where it serves as a defense barrier against foreign substances. In order to prevent the majority of substrate medications from being reabsorbed into the cells, they may be processed by being pumped out of the intestinal cells into the lumen via P-gp. Numerous medications' bioavailability is constrained by this mechanism (Gibson and Skett, 2001). Additionally, it can result in drug interactions, particularly when medications are designed to inhibit P-gp or CYP3A4 (Thummel, 2007).

2.3 Advantages of oral drug delivery

Oral route is a popular route since its non-invasive, with a high rate of patient compliance, easy to handle, and does not require any special sterile conditions. Oral route is the most simple and convenient, cost-effective method as no other external devices are needed or medical personnel is required for administration. This mode of administration is painless as the patient needs to swallow the medicine and the patient can do it by him/herself and requires no assistance which means self-administration is possible. This method is suitable for frequent and long-term use (Gajdacs, 2019).

2.4 Disadvantages of oral drug delivery

Though oral drug delivery has many advantages, it is also associated with a number of disadvantages. For instance, oral drug delivery strategy is not suitable for emergency purposes because it cannot give initial onset of action as it takes a considerable time to reach the systemic circulation to give a therapeutic effect. (Talevi, 2018)

Patients with consciousness can only take oral drugs as patients have to swallow the drug. Hence, those who are unconscious or unable to swallow drugs cannot take oral medications. Additionally, oral drug administration requires patient's co-operation or compliance and patients who are vomiting and is suffering from diarrhoea in a severe stage are also not advised to take oral drugs. (Raj, 2019)

Oral drug delivery system is not suitable for those drugs which are unpalatable and highly irritating. Some drugs are destroyed in the GIT environment for example, insulin. Drugs like lignocaine and imipramine have extensive first pass metabolism. Therefore, these category drugs are not suitable for oral preparations (Talevi, 2018), (Raj, 2019).

Drug-drug interactions and interactions with other substances present in the GI tract such as gastric juices results in changes in solubility of the drug. One such example has been observed by decrease in absorption of tetracycline resulting from the formation of insoluble calcium complexes due to interaction between the drug or its formulation additives with dairy products (Gajdacs, 2019).

Chapter 3

Treatment via Pulmonary route

3.1 Pulmonary drug delivery strategy

For the treatment of respiratory illnesses, inhaled drugs are a prominent drug delivery method over the last few decades. This route of administration allows a drug to be administered to the site of action directly at a lower dose compared to oral dosage forms, thus reducing dose-related adverse effects with a rapid onset of action resulting in greater therapeutic efficacy (Traini & Young, 2009).

Pulmonary drug delivery is a method that involves medication to inhale through the lungs. Then also allows the medication to enter the bloodstream through the alveolar epithelium. It is a non-invasive alternative to subcutaneous and intravenous injection. Delivery devices for pulmonary delivery plays a significant role in the efficiency. Nebulizers, metered-dose inhalers (MDI) and dry powder inhalers (DPI) are the popular pulmonary delivery devices to achieve targeted treatment. The nature of drug, formulation, site of action and pathophysiology of the drug are taken under consideration while choosing a device (Nanjwade et al., 2011).

3.2 Classification of Pulmonary drug delivery systems

Inhalation devices are generally of three types - the dry powder inhaler, the pressurized metered dose inhaler, and the nebulizer.

3.2.1 DPI

Dry powder inhaler (DPI) delivers a small dose about micro- to milligram range, a metered and aerosolized quantity of drug, into the patient's lungs. To treat various types of respiratory

diseases like asthma and other inflammatory and infectious lung diseases as well as disorders like diabetes, cancer, neurological disease. Efficiency of these devices however rely on the patient's effort to aerosolize the powder aliquot because of lack in internal energy source. Different types of energy are provided by active devices for aerosolization for instance, a loaded spring and compressed air provide kinetic energy, while a battery provides electric energy. [9] For lower frequency of drug intake, DPI may be a suitable option.

However, the balance between flow rate and inhaler resistance the device is a drawback in the design of dry powder inhalers. A faster airflow is required for increased particle deagglomeration in dry powder inhalers, and greater impactions make it possible to attain a maximum therapeutic efficacy defined by fine particle fraction. Difference in air flow resistance of DPI devices controls the required inspiratory effort by the patient. In order to get the maximal dose from the inhaler device, the inspiratory flow rate must be properly generated, which becomes challenging as the device's resistance increases. (Chandel et al., 2019)

3.2.2 pMDI

Metered dose inhalers (MDI), also known as pressurized metered dose inhalers (pMDIs), are the most popular delivery mechanism for aerosol medications. MDI and pMDIs have several advantages, including portability, the lack of an external power source, and the delivery of a fixed dose. pMDIs is a preferred choice of inhalation device for administering drugs such bronchodilators, antibiotics, anti-inflammatory agents, analgesics and anti-cholinergic drugs. (Chandel et al., 2019). pMDI or pressurized metered-dose inhalation is used for delivering drugs in a simple and reliable multi-dose way. The container, propellants, formulation, metering valve, and actuator all play specific role in the creation of the spray and thus determine drug delivery to the lungs in the pMDI device. The pMDI container must endure the propellant's high pressure. Stainless steel has been used as the material for pMDI containers.

Aluminium is presently the favoured material since it is lighter, more compact, less fragile, and light-proof than glass. Coatings on internal container surfaces may be beneficial in preventing medication particle adherence and chemical degradation. pMDIs contain drugs either in the form of particle suspensions or solutions. (Nanjwade et al., 2011)

3.2.3 Nebulizer

A nebulizer is a device that delivers medication to patients in the form of a mist that they inhale. In other words, nebulizer produces a mist from liquid medicine. The process is, nebulizer transforms liquid medicines into small droplets which result in aerosol or spray. Hence, it becomes very easy to breathe into the lungs. Cystic fibrosis, asthma, and other respiratory illnesses are routinely treated with it. Jet and Ultrasonic nebulizers are the two main types of nebulizers (Nanjwade et al., 2011).

3.3 Barriers to pulmonary drug delivery

3.3.1 Mechanical barriers

Chemical, mechanical or immunological barriers might be thought of as lung defense mechanisms that an inhaled drug particle can come into contact with (Box 1) (Patel, 2015). The conducting (tracheobronchial) airways of the lungs, the alveolated airways, and the extrathoracic airways make up the human respiratory system (Figure 1). The upper airways (nasal and oropharyngeal), that are small, angled channels with a range of sizes, are ideal locations for inertial impaction, which stops particles from entering the lungs (Darquenne, 2015). It is best to breathe in through the mouth for delivery into the lungs because the nasal passages serve as a particularly effective aerosol "filter." The lungs are made up of an intricate web of branching airways known as the "bronchial tree." A particle must cross several airway

bifurcations where it may potentially be deposited in order to reach the alveolated region and reach the big epithelial target site.

An aerodynamic diameter of 5 um is necessary to deliver medications to the entire lung (Newman SP., 2015). Deposition, is also highly dependent on inhalation factors, including inhaled flow velocity, inhaled volume, and breath-hold time. For medications delivered via pMDI, the inhaled flow rate must be slow (Arora D, 2006) but for medications delivered via DPI, a "quick," "fast," or "forceful" inhalation is typically advised in patient instruction leaflets because the shear forces produced by such an inhalation are utilized for distribute the medication powder and ensure a comparatively elevated inhalable dose (Chrystyn, 2015). Less than 20 percent of total of the dose is typically deposited in the lungs by most inhalers (Borgstrom,2006) and with bulk typically being maintained in the device or the oropharynx (for pMDIs and DPIs) (for nebulizers). In disease, where airways may be restricted by bronchoconstriction, mucus hypersecretion, and inflammation, or may even be obstructed by plugs of mucus, mechanical barriers are more noticeable (Figure 1). A gel layer sits on top of a liquid layer that contains cilia in lung mucus. A natural lung defense system called lung mucociliary clearance removes accumulated items from the conducting airways and transports them to the oropharynx where they are either ingested or expectorated (Ganesan S, 2013). Within 24 hours, the tracheobronchial airways of a healthy lung are free of any deposition. Mucociliary clearance may be advantageous if it directs deposited medication toward target sites from unfavorable locations, but it may be harmful if it directs drug away from target sites.

Box 1. Barriers to Pulmonary Drug Delivery

Barriers to pulmonary drug delivery.
Mechanical barriers • Droplets and particles of drug residue inhalation in the mouth and nose • Large airway obstruction losses limit supply to peripheral lung areas. • Airway constriction, excessive mucus production, and mucus clogging are all symptoms of illness. • Drug withdrawal by lung mucociliary clearance **Chemical barriers** • The breakdown of drugs by proteolytic enzymes • Effects of other substances, such as surfactants • immune system restrictions • Alveolar macrophage engulfment of particles **Behavioural barriers** • noncompliance with treatment plan • Poor inhaler technique

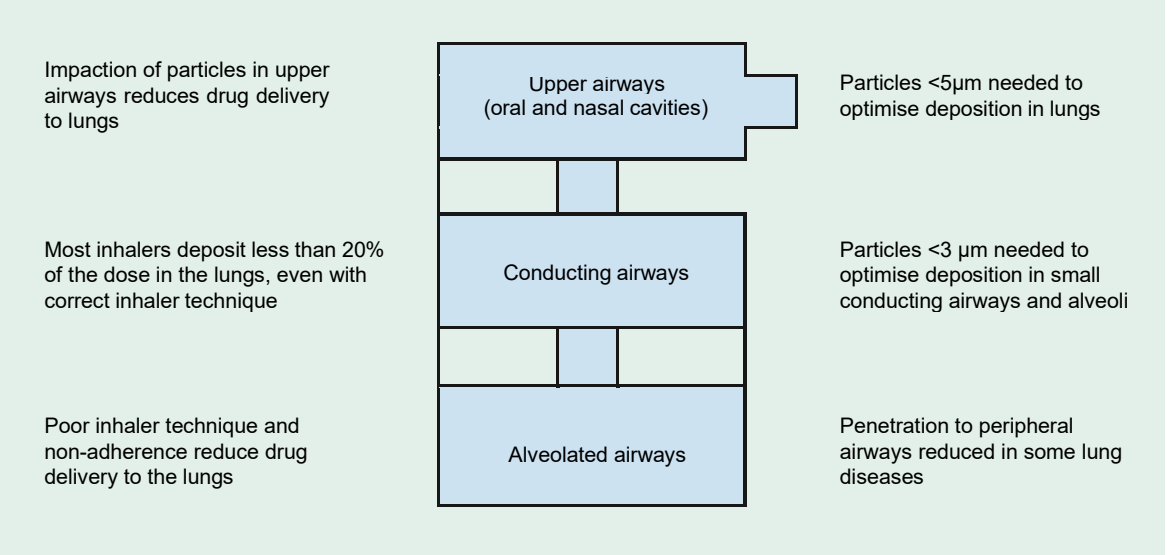

Figure 1. Schematic representation of the different parts of lungs and factors affects drug delivery to the lungs.

3.3.2 Chemical & immunological barriers

Although this mechanism is not well understood, it is anticipated that deposited particles will disintegrate in lung fluids once they are inside the lungs (Patton, 2010). The drug should theoretically be available to exert a local impact in tissue or be absorbed into the systemic circulation, assuming mucociliary clearance has not removed it (Figure 2). Unfortunately, agents such as surfactant and proteolytic enzymes (proteases) may negatively affect medications that have been deposited. Proteins and peptides in the lungs may be hydrolyzed by proteolytic enzymes, such as neutral endopeptidase and cathepsin H, rendering them inactive (Labiris, 2003) (Patton, 2010). Alveolar macrophages, the main phagocytic cells guarding against inhaled particles, may come into contact with undissolved drug particles (Labiris, 2003). An immune barrier made up of alveolar macrophages does not differentiate between potentially dangerous and potentially beneficial compounds (Patel, 2015). Drug particles could be taken up by macrophages and removed from the lungs, perhaps through the lymphatic system or by moving them to the bottom of the mucociliary escalator. In animal models, the impacts of macrophages on medication absorption have been shown, but it is less clear how they function in humans (Patton, 2010). Inhaled particles may not stick to the lung surfaces as a result of surfactant, making them more accessible to macrophages (Patel, 2015).

For drugs delivered by the majority of inhalers, mechanical, chemical, and immunological barriers together result in low pulmonary bioavailability (for locally acting drugs) and systemic bioavailability (for systemically acting drugs); therefore, it may be desirable to develop new, more effective inhaler systems to lessen the effects of these barriers (Cipolla, 2016).

3.3.3 Behavioral barriers

3.3.3.1 Adherence

What patient do or don't do with their inhaler devices has a significant impact on how well drugs are delivered into the lungs (Newman, 2014). The number of doses consumed, stated in relation to the number of doses prescribed, can be used to define adherence (Kikidis D, 2016). A patient may feel well and choose not to take the prescribed medicine, or they may merely forget to take it (Rau JL, 2005). Nonadherence to the therapeutic regimen is widespread and may be purposeful or unintentional. Levels of adherence are affected by cultural variables and myths. For instance, a poll conducted in India found that 85% of respondents thought using an inhaler carried a social stigma and that a comparable amount thought inhalers were only effective for treating serious illnesses (Gupta, 2011).

3.3.3.2 Inhaler technique

Poor inhaler technique has long been acknowledged as a barrier to effective inhaled medicine delivery, and alarmingly, a recent assessment found that patients' proficiency with inhalers has barely changed over the past 40 years. Major mistakes in inhaler technique for pMDIs include failing to inhale deeply and gently, as well as failing to actuate the inhaler while breathing in (bad coordination). For DPIs, the main issues are inadequate inhalation force as well as device-specific handling and preparation mistakes, such as improper device alignment. The majority of patients are able to utilize a DPI strongly, however certain elderly patients may not have the strength in their inspiratory muscles needed to properly operate a DPI (Malmberg, 2010). Both types of inhalers have issues with incomplete exhalation before inhalation (Sanchis, 2016) and an insufficient breath-hold time following inhalation (Chrystyn, 2016). Patients still need to be trained on how to use assemble the nebulizer equipment and while using nebulisers to avoid

coughing or breathing through their nose to eliminate the chances of reduced therapeutic response (Ne.wman SP., 2014).

3.3.3.3 True adherence

Noncompliance and ineffective inhaler technique result in inadequate and highly variable lung deposition (Newman SP., 2014), which can lead to less well-controlled illness, more frequent trips to the ER, and a greater financial burden on the healthcare system (Al-Jahdali, 2013) (Lewis, 2016). Inhaled medicine delivery has allegedly underperformed as a result of inadequate attention being paid to these problems. As a result of poor adherence and improper inhaler technique, the phrase "true adherence" (or "real compliance") has evolved for successful disease management in the future (Everard, 2014).

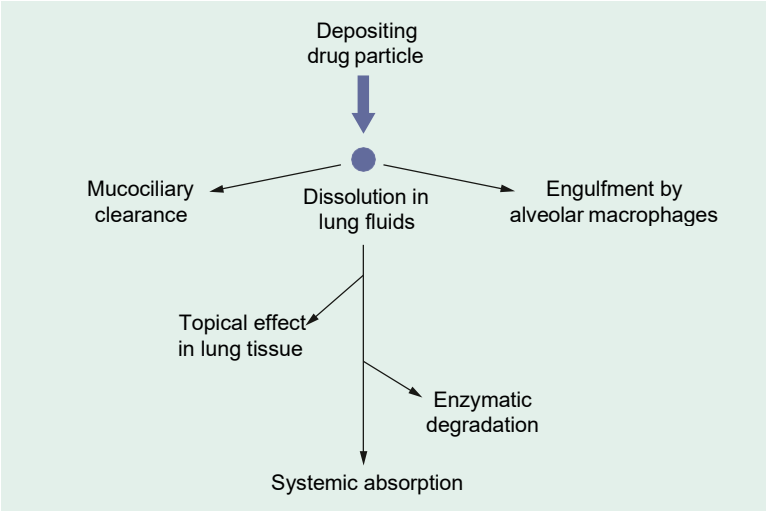

Figure 2. Schematic diagram showing the fate of deposited inhaled drug particles

3.4 Advantages of pulmonary drug delivery

The lung has a large surface area, supplied by a rich blood capillary network, enabling rapid uptake and absorption of the drug in the lung and solute transport. Therefore, the drug reaches the site of action directly with minimal exposure to extracellular enzyme levels for metabolic breakdown thus surpassing the extensive first pass effects by the liver enzymes associated with the oral route of drug administration. Consequently, pulmonary route of drug administration offers enhanced bioavailability along with being non-invasive. The pulmonary route allows targeted drug delivery to the site of action. Importantly, a much lower dose is required to elicit a therapeutic response compared to oral mode of drug administration, thus reducing the risk of toxicity and dose-related adverse effects (Alqahtani et al., 2021).

3.5 Disadvantages of pulmonary drug delivery

Even though the pulmonary route offers a wide range of advantages, yet it is associated with a few disadvantages. Some drugs given via the inhaled route may result in irritation and therefore must be closely monitored if given using pulmonary drug delivery devices. The major drawback using inhalation route is that the drug is exposed to various mechanical, chemical and immunological barriers and the defence and clearance mechanisms act on the inhaled drug particles to propel them out of the lungs once they are deposited within the respiratory tract. Hence, the transport of inhaled drugs across the lung epithelium is a crucial aspect that needs to be investigated to determine the efficacy of the inhaled drug. Additionally, pulmonary drug delivery is adversely affected due to poor inhaler technique by the patients that directly affects the therapeutic response of a drug. As a result, patients need to be trained for better hand coordination while using the inhaler devices (Alqahtani et al., 2021).

Chapter 4

Conclusion and Perspectives

Drug distribution through the lungs is more complicated than just swallowing a tablet. The respiratory system has defense clearance mechanisms that may drive the inhaled drug particles out of the lungs before it can produce a therapeutic effect. The majority of inhaler devices only deliver a small portion of the dose to the lungs which is advantageous as it overcomes side-effects associated with higher dose of drugs as observed with oral route. Small doses of drugs delivered to the lungs is not a problem for inhaled medications used to treat asthma and other respiratory diseases. However, drug delivery strategies needs to be optimised for other inhaled drugs such as antibiotics, analgesics, and peptides that is required to produce a systemic effect (including insulin) to increase the bioavailability of these therapeutic agents. Furthermore, each patient must learn how to operate an inhaler device, which is a major hindrance of pulmonary drug administration. Poor inhaler technique and poor adherence to inhaled regimens continues to be a serious disadvantage of pulmonary drug delivery with substantial negative clinical and financial effects, although they can be partially addressed by technological advances and partially by better patient education. It is crucial to choose an inhaler that the patient will use and understands how to use properly.

The most popular and convenient method for administering medication to both adult and paediatric patients is orally. Although orally delivered drugs possess the advantages of convenient way of administering the drug resulting in enhanced patient compliance, portability and ease of large-scale manufacturing, they undergo extensive first-pass metabolism resoling in decreased bioavailability and reduced therapeutic efficacy with slow onset of action. Advanced formulation solutions may be able to solve problems and difficulties that conventional oral formulations can cause due to poor solubility issues. Utilizing nanocarriers

to enhance medication solubility, permeability, and bioavailability is one such tactic. It is necessary to have a better understanding of how common diets affect patients' individual drug absorption rates. The change from a fed to a fasted state is frequently ignored in extensive preclinical research, which may have an impact on the mechanism and pace of drug absorption. The development of *in vitro* models that can correlate with the *in vivo* performance of the therapeutic agents are crucial to predict the therapeutic efficacy of both oral and inhaled drugs. This will certainly decrease the time for the transition of formulations from the bench to bedside to increase the standard of care. When developing novel formulations, the intended patient population must also be considered. The use of safe and efficient excipients must be taken into account in future research using nanocarrier technology to develop both oral and pulmonary therapeutic formulations. Formulation development and excipient screening will continue to advance as the landscape of delivery methods evolves. To sum up, if current challenges and barriers discussed could be overcome then the total amount of time needed to produce a novel formulation or optimize current formulations will be less than the current time needed to develop better and more potent drug formulations.

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