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Pharmacokinetic/ pharmacodynamic evaluation of inhalation drugs: application to targeted pulmonary delivery systems

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Inhaled therapy with either glucocorticoids and/or β_2-adrenergic drugs remains the mainstay of asthma treatment. In the last few years, a number of new products have been introduced into the market with the goal of improving efficacy and safety. This review article summarises the pharmacokinetic and pharmacodynamic properties of inhaled drugs for topical delivery necessary to achieve this goal. Pharmacokinetic properties include a high pulmonary deposition, low oral bioavailability, optimised pulmonary residence time and a very high systemic clearance. Optimisation of pharmacodynamic properties, such as receptor selectivity, may also yield drugs with improved pulmonary selectivity. As existing drugs also provide high efficacy and safety profiles, future developments will represent only slight improvements and quantum leap improvements are unlikely to occur.

Keywords: pharmacodynamics, pharmacokinetics, pulmonary selectivity

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1. Introduction

1.1 Asthma

Asthma is a chronic inflammatory disease of the airways, which is characterised by hyperresponsiveness, reversible airflow limitation and respiratory symptoms [1-4]. It is the most common chronic lung disorder in the world, and its prevalence is steadily growing [2,5]. It has been estimated that in the US alone, the total amount spent on treating asthma has approached $6 billion/year [6,7]. Patients afflicted with asthma exhibit shortness of breath, severe coughing, chest tightness and a decrease in expiratory airflow [4,5], with the severity of their condition ranging from mild to life threatening.

1.2 Treatments for asthma

Several different therapies are currently in use for the treatment of asthma. Short-acting β-agonists such as albuterol, metaproterenol and terbutaline act quickly and are useful for emergency treatment. Long-acting β-agonists such as formoterol and salmeterol are currently used for inhalation asthma treatment. Long- and short-acting β_2-agonists are effective bronchodilators, which act by relaxing the airway smooth muscle, thus allowing air to flow into the lungs [8]. Although long-acting β_2-adrenergic drugs show beneficial effects together with glucocorticoids, they mainly prevent symptoms and do not actively attack the causes of the disease.

Another class of drugs found to show clinical efficacy are leukotriene receptor antagonists such as montekulast and zafirlukast, which are given orally because of their minor systemic side effects. These drugs act by inhibiting bronchoconstriction by blocking the

Table 1. Important factors in pulmonary targeting.

Pulmonary components	Systemic components
Efficiency of pulmonary deposition	Oral bioavailability
Location of pulmonary deposition	Clearance
Pulmonary absorption rate	Volume of distribution
Pulmonary residence time	Plasma and tissue binding
Lung tissue binding	
Pulmonary pharmacodynamic characteristics	Systemic pharmacodynamic characteristics

leukotriene-related pathways. They may also possess some anti-inflammatory effects; however, the extent of their anti-inflammatory action is limited [9]. Other inhalation drugs used to treat asthma are the anticholinergic drugs and the NSAIDs such as nedocromyl sodium. Despite the availability of these agents, glucocorticoids represent the cornerstone of asthma therapy as they act on the basic underlying inflammatory events involved in asthma [10]. Glucocorticoids, β_2-adrenergic and anticholinergic drugs, as well as nedocromyl sodium, are generally delivered via inhalation to achieve distinct pulmonary effects with reduced systemic side effects. This is the case as inhalation therapy warrants high drug concentration in the lung, whereas systemic concentrations are reduced. This results in limited systemic side effects, whereas the antiasthmatic effects are maintained. However, it should be mentioned that asthma drugs present in the systemic circulation may also contribute in part to the beneficial antiasthmatic effects, and it remains to be quantified whether the systemic presence of antiasthmatic medication may be beneficial, at least in some cases of severe asthma. This report, however, concentrates on pharmacokinetic (PK)/pharmacodynamic (PD) relationships that optimise pulmonary selectivity, as a means to reduce systemic drug levels while maintaining pharmacologically relevant drug concentrations in the lung. Currently employed drugs include beclomethasone dipropionate, flunisolide, triamcinolone acetonide, budesonide and fluticasone propionate. Mometasone furoate and ciclesonide have been approved in Europe, but approval in the US is still pending. These drugs are considered the mainstay of asthma treatment due to their high degree of clinical effectiveness by controlling the underlying disease factors. This results in controlling the symptoms of asthma and improving lung function, as well as preventing exacerbations and attenuating changes in airway structure [11-16].

Drugs used to treat asthma, with the exception of leukotriene antagonists, are usually administered via the inhalation route. This method is considered advantageous compared with therapeutic agents given orally, due to the delivery of drug to where it is most needed (i.e., the lungs [17]). In addition, the pharmacological effect of the drug is observed relatively early with inhaled bronchodilators. Finally, smaller doses can be given with inhaled drugs compared with oral drugs, thus potentially minimising harmful side effects [18]. Pulmonary drug delivery has been successfully utilised for topical therapy to treat asthma, with the aim of obtaining a high degree of pulmonary targeting, thus inducing a significant pulmonary effect while at the same time minimising systemic side effects. The PK and PD characteristics of the drug largely determine the degree of pulmonary targeting (**Table 1**). These factors can be divided into pulmonary and systemic components. The pulmonary PK factors include how much of the inhaled drug is deposited into the lung and in which region of the lung the drug is deposited. The dissolution or release rate and/or absorption rate of the drug into pulmonary cells, and finally systemic circulation, are relevant because they determine the residence time of the drug in the lung. The extent of pulmonary tissue binding has to be considered as it impacts how the free pulmonary drug concentration will relate to the pulmonary effect. Finally, one has to consider the mucociliary transport as a removal mechanism for solid particular drug from the upper portion of the lung.

The systemic components relevant to pulmonary targeting include how much of the inhaled drug is swallowed following administration, and its oral bioavailability [19]. The systemic clearance of the drug, as well as its tissue and plasma protein binding, are also pertinent factors. With respect to both pulmonary effects and systemic side effects, PD properties have to be considered.

This review will explore further the PK and PD properties of inhaled antiasthmatic drugs, with a special focus on inhaled glucocorticoids and how these properties relate to their pulmonary targeting. Although the focus of this review is on drugs used to treat asthma, the concepts and mechanisms for pulmonary targeting are identical for other pulmonary diseases such as chronic obstructive pulmonary disease and cystic fibrosis.

1.3 Pharmacokinetic/pharmacodynamic model used to describe pulmonary targeting

Figure 1 shows the succession of events that are relevant for pulmonary drug administration. Immediately after inhalation of the drug, a portion of the dose (respirable fraction) will be deposited into the lungs. The larger particles will impact on the oropharyngeal region and are subsequently swallowed. This portion of drug will then be absorbed across the gastrointestinal (GI) tract and be subject to first-pass metabolism by the liver before entry into the systemic circulation. The model that will be used in this review assumes that the fraction of drug that is metabolised during the first pass is not pharmacologically active, and hence will not induce any systemic effect. The amount of drug that will be absorbed across the GI tract will depend on how much drug reaches the tract and the oral bioavailability of the drug.

For a drug that has been deposited in the lung, there are two competing processes controlling the fate of the drug particles, which play a key role in pulmonary targeting. The

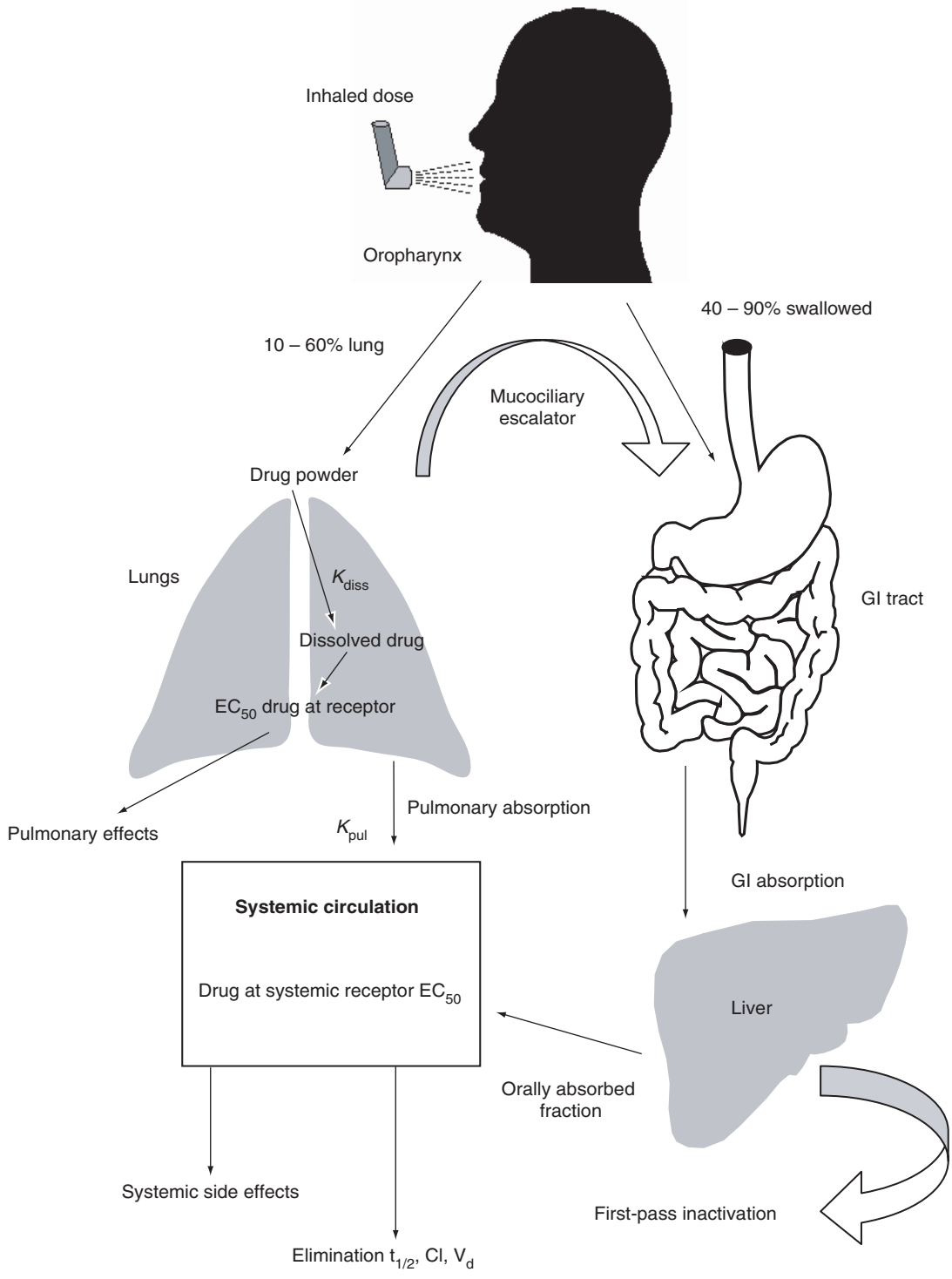

Figure 1. Pharmacokinetic/pharmacodynamic model used to describe pulmonary targeting.
Cl: Clearance; EC_{50}: Effective concentration for half-maximum response; GI: Gastrointestinal; K_{diss}: Rate of dissolution; K_{pul}: Rate of pulmonary absorption; $t_{½}$: Half-life; V_d: Volume of distribution.

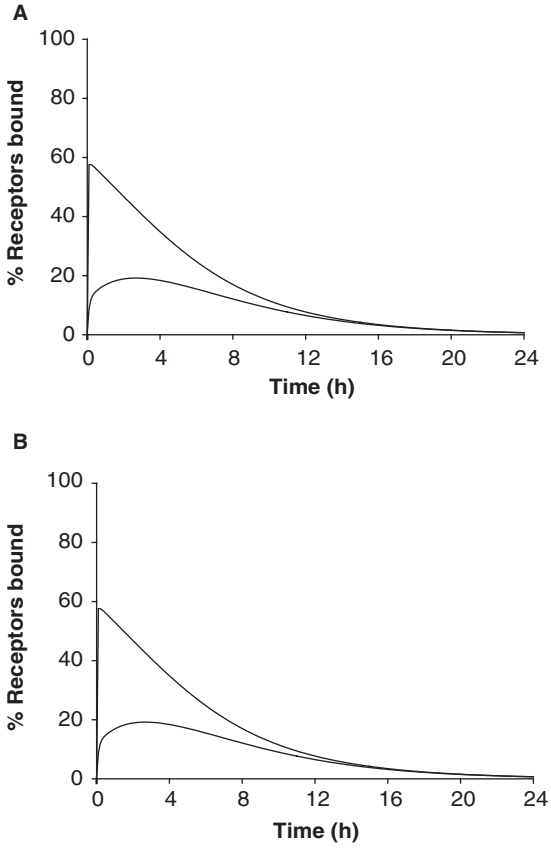

Figure 2. Effect of receptor affinity on model-predicted pulmonary (lower line) and systemic (upper line) receptor occupancies. Pulmonary targeting, the difference between pulmonary and systemic receptor occupancies, was observed after two drugs were administered with differing EC_{50} values (a measure of receptor binding affinities). Differences in receptor binding affinities can be resolved by adjusting the dose; **A.** EC_{50} (lung, systemic) = 0.1 ng/ml dose: 750 µg; **B.** EC_{50} (lung, systemic) = 0.033 ng/ml dose 250 µg. All other parameters (e.g., clearance, volume of distribution) were fixed during the simulations.
EC_{50}: Effective concentration for half-maximum response.

first is the dissolution of the drug into the lung-lining fluid followed by its uptake into the pulmonary cells. The second is the removal of solid drug particles from the upper part of the lung by mucociliary transport or in the alveolar region by macrophage uptake. Only unbound drug that is localised in the lung region can exert pulmonary effects. Thus, pharmacologically relevant pulmonary drug levels will be determined by the complex equilibrium between the mucociliary clearance rate, dissolution rate of solid particles (if applicable) and absorption into the systemic circulation. It is important to note that the drug that is dissolved in the lungs will be absorbed into the systemic circulation. The amount of systemic exposure will be dependent on the amount of drug absorbed from the lungs as well as the GI tract, and on the ability of the body to remove the drug via clearance and metabolic processes [20].

A previously described PK/PD model [21] will be used for visualising the effects of individual PK and PD factors on pulmonary targeting by converting free-drug concentrations in the lung and the systemic circulation into the PD relevant degree of pulmonary and systemically occupied receptors (**Figure 1**). This model enables the visualisation of the degree of pulmonary targeting over time by observing the difference between the desired pulmonary receptor occupancies and unwanted systemic occupancies as surrogate markers of the effect and side effects.

2. Pharmacodynamic factors in pulmonary targeting

For inhaled glucocorticosteroids the degree of effects and side effects seems to be related to the degree of receptor occupancy [22-24], which again is determined by the free-drug concentration in the given tissue and the receptor binding affinity of the drug. For β_2-adrenergic drugs, correlations were found between *in vitro* indicators of drug activity in cell culture and the observed pharmacological activity *in vivo* [25,26]. Thus, receptor binding affinities or other *in vitro* parameters can be used when describing the pharmacological properties of inhaled glucocorticoids and β_2-agonists in the lungs. In order to understand the significance of receptor occupancy of the drug with regards to pulmonary targeting, two distinct cases must be examined. The first case, observed with glucocorticoids, is found when the pulmonary (wanted) and systemic (unwanted) effects are controlled by the same receptors in pulmonary and systemic tissues. Thus, the contrast between the lung and systemic receptor occupancy (i.e., pulmonary targeting) is not influenced by any differences in receptor binding affinities. Therefore, a drug exhibiting a lower receptor binding affinity can show the same degree of pulmonary targeting as a drug with a higher receptor binding affinity when the dose is adjusted accordingly (**Figure 2**). These relationships are also supported by PK/PD studies investigating the effects of exogenous glucocorticoids on lymphocyte and cortisol suppression. Differences in the activity at the site of action mirror differences in the receptor binding affinity. This supports the statement that pulmonary selectivity cannot be achieved with PD modulations of inhaled steroids. It should be mentioned, however, that recent research seems to suggest that effect and side effects can be separated on a PD level, as newer glucocorticoids seem to induce desired effects by transrepression (blockage of transcription factors such as activator protein-1 and NF-κB), whereas the induction of the undesired side effects through transactivation (induction of the synthesis of side-effect-inducing proteins) is reduced [27,28]. This observation seems to suggest the possibility of optimising the PD profile of inhaled glucocorticoids.

When the pulmonary desired effects and side effects are controlled by different receptors (**Figure 3**), as seen with β_2-adrenergic drugs, drugs with high selectivity should be

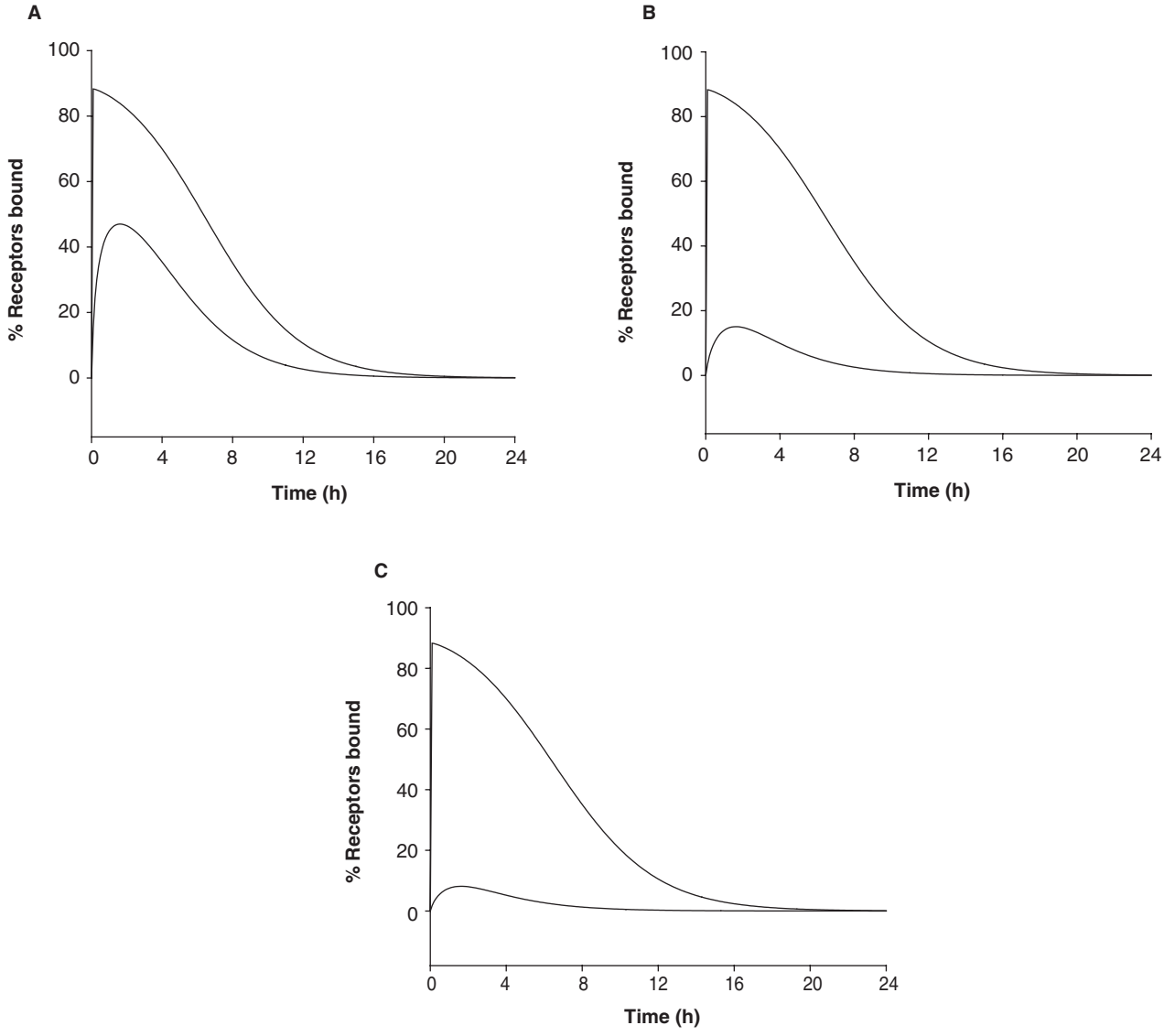

Figure 3. Pulmonary (upper line) and systemic (lower line) receptor occupancies for a drug that produces pulmonary and systemic effects by binding to two different types of receptors. The receptor affinity of the drug in the lung remains the same in all cases, but decreases with the systemic organs. **A.** EC_{50} (lung) = 0.01; EC_{50} (systemic) = 0.01; dose = 500 µg; **B.** EC_{50} (lung) = 0.01; EC_{50} (systemic) = 0.05; dose = 500 µg; **C.** EC_{50} (lung) = 0.01; EC_{50} (systemic) = 1; dose = 500 µg.
EC_{50}: Effective concentration for half-maximum response.

chosen for therapy. Currently, a number of long- and short-acting β_2-adrenergic drugs show high selectivity towards the β_2-adrenergic receptor, and this selectivity is important for the pharmacological safety profile and lung selectivity.

In addition, PD properties towards other steroid receptors should be assessed within this context. As an example, some newer, lipophilic glucocorticoids also show significant binding affinity towards the progesterone receptor [29] with binding affinities equivalent to that of the glucocorticoid receptors. Thus, such steroids would be able to induce progesterone-related side effects if glucocorticoid-related effects are seen systemically.

3. Pharmacokinetic factors in pulmonary targeting

As shown in **Table 1**, a number of PK properties are vital for pulmonary selectivity and these are discussed in the following section.

3.1 Oral bioavailability

The amount of systemic exposure of an inhaled drug is dependent on the quantity of drug that is absorbed by the pulmonary and oral routes. A significant percentage of drug given by a metered-dose inhaler (MDI) or dry powder

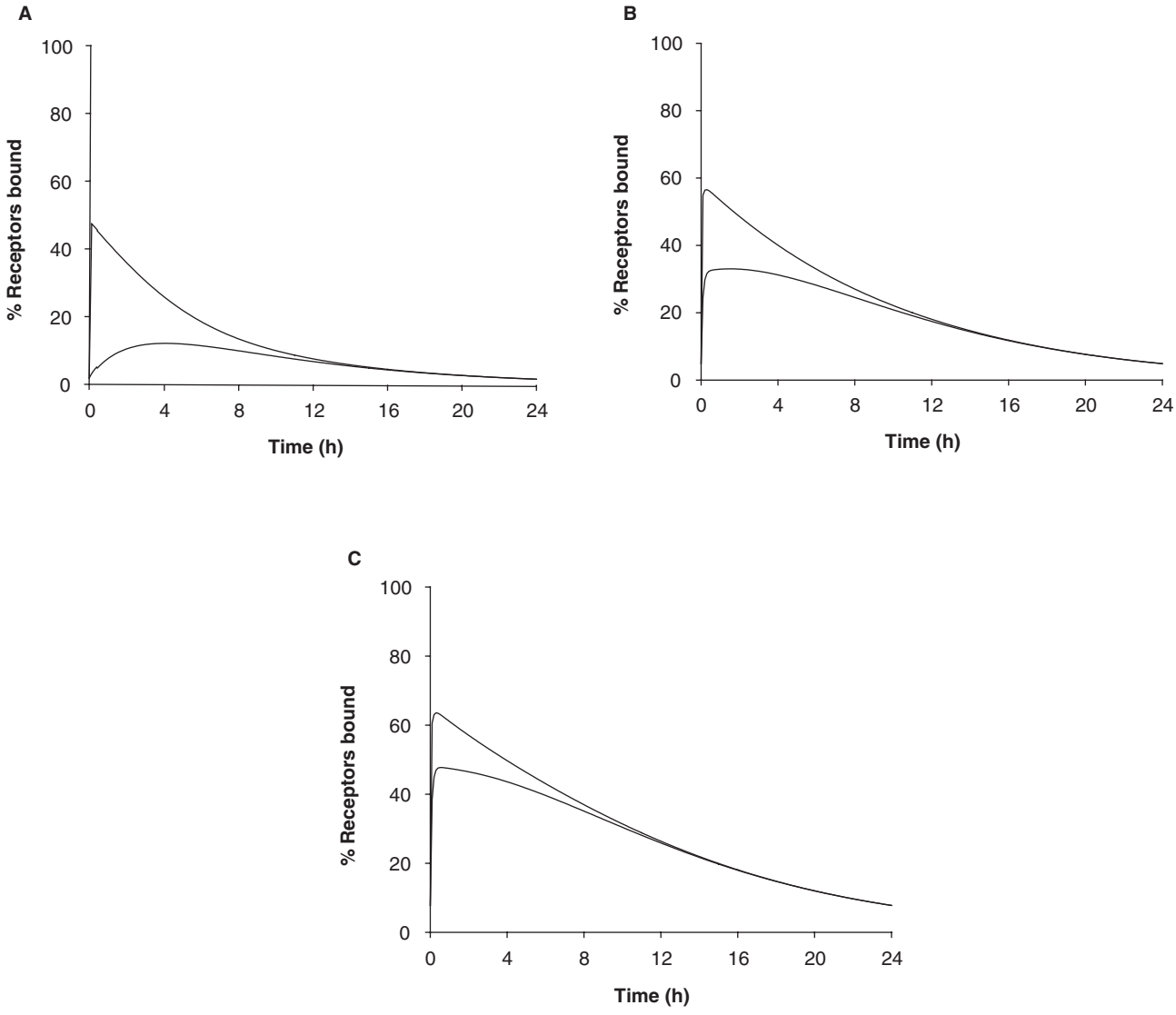

Figure 4. Simulations showing the effect of oral bioavailability on pulmonary (upper line) and systemic (lower line) receptor occupancies. The values of F change in each case: 1, 50 and 100% in **A**, **B** and **C**, respectively. All other relevant parameters remain constant.
F: Oral bioavailability.

inhalation (50 – 90%) reaches the GI tract, and is available for oral absorption. The overall amount of drug that is available for oral absorption is dependent on how much is delivered to the oropharynx and subsequently swallowed and how much drug in the lungs is cleared by the mucociliary clearance escalator, as this fraction will also be reaching the GI tract. The oral bioavailability is mainly determined by the hepatic or prehepatic first-pass effect, which serves as the final gatekeeper in determining how much drug will enter the systemic circulation from the GI tract and cause any unwanted side effects. Therefore, an ideal drug candidate for inhalation therapy should possess the lowest possible oral bioavailability. The newer inhaled corticosteroids have low oral bioavailability that are < 15% (fluticasone propionate < 1%, budesonide 12%, mometasone furoate < 1%) [30,31]; whereas older inhaled steroids, such as flunisolide, triamcinolone acetonide and beclomethasone dipropionate, show an oral bioavailability in the range of 20 – 40% [32-35]. Short-acting β_2-adrenergic drugs also have varying bioavailabilities in the range of 1.5 – 50% [26]. The effect of changing the oral bioavailability of a drug on pulmonary and systemic receptor occupancies is shown in Figure 4. These relationships indicate that, especially for inhalers with high oropharyngeal deposition, oral bioavailability needs to be small for achieving pulmonary selectivity. So far, most of the inhaled glucocorticoids in development show oral bioavailabilities of < 1% and, consequently, systemic side effects are not mediated through

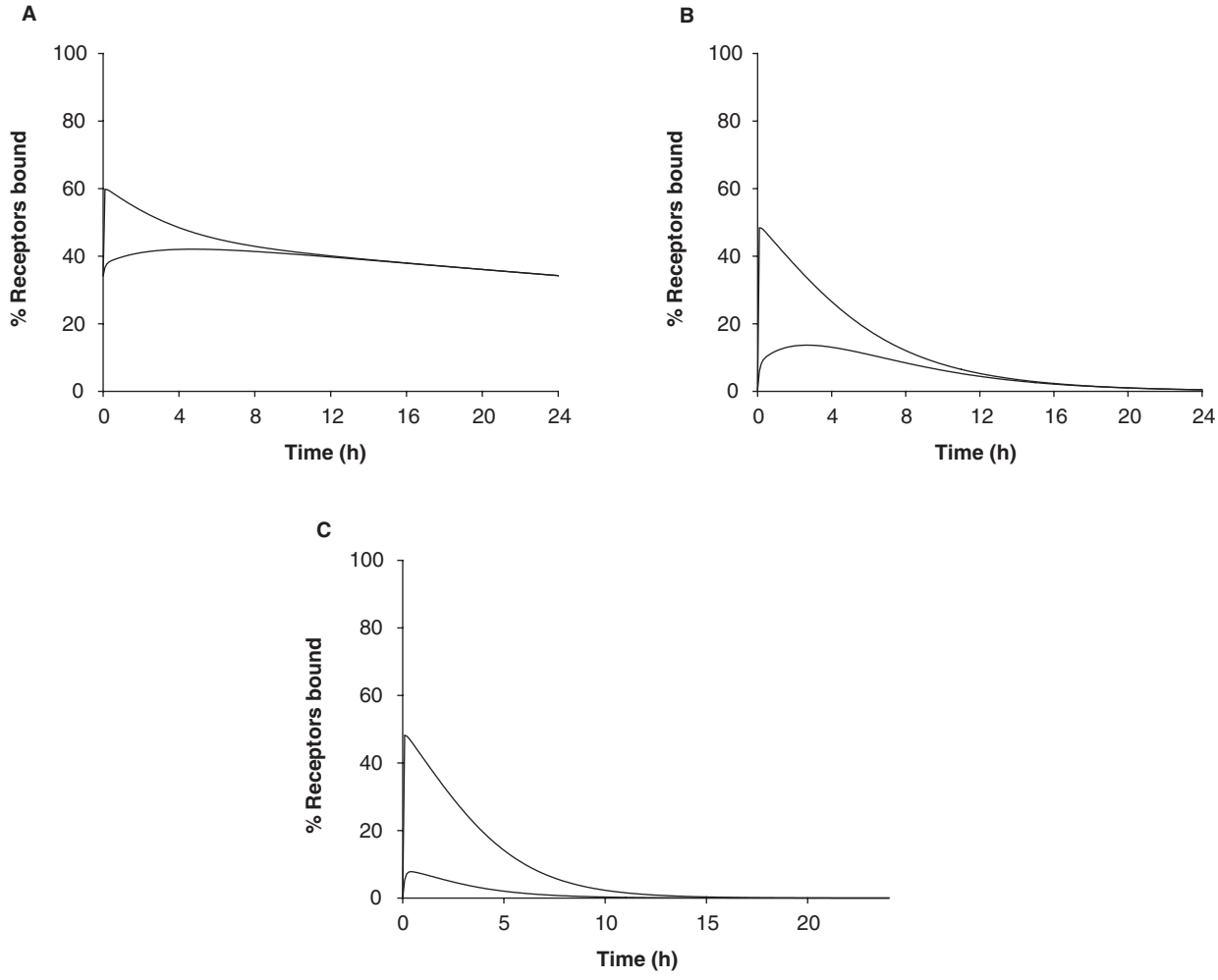

Figure 5. The effect of systemic clearance on pulmonary (upper line) and systemic (lower line) receptor occupancies. Simulations are shown for Cl values of 10, 100 and 500 l/h in **A**, **B** and **C**, respectively. All other parameters remain unchanged.
Cl: Clearance.

orally swallowed drugs. Some of the older short-acting β_2-adrenergic drugs show oral bioavailabilities in the range of 20 – 50% [36] and improvements with respect to this parameter are still possible.

3.2 Systemic clearance, volume of distribution

Systemic clearance is a primary PK parameter that addresses the ability of the body to eliminate drug that has been absorbed into the systemic circulation. The cumulative systemic exposure, as shown by the area under the plasma concentration–time profile, is represented by the total amount of drug entering the systemic circulation and the systemic clearance. Therefore, if a drug taken by inhalation has a high rate of systemic clearance, it will have a reduced systemic exposure. **Figure 5** depicts the relationship between systemic clearance and the degree of pulmonary targeting. The simulations show a positive correlation between an increase in systemic clearance and an increase in pulmonary selectivity. Hence, an ideal drug candidate for inhalation therapy should possess a high systemic clearance so as to avoid any potential unwanted systemic side effects. Most of the inhaled glucocorticoids are efficiently cleared in the liver through metabolic inactivation. Thus, most of the inhaled glucocorticoids have clearance values close to the liver blood flow: ~ 90 l/h in a healthy individual. New drug developments have evaluated the possibility of extrahepatic clearance as a way to further increase pulmonary selectivity. Although metabolic inactivation in the blood would be of significant clinical value, it has been difficult to design glucocorticoids that show sufficient stability in the lung while being efficiently inactivated in the blood [37].

Another primary PK parameter is the volume of distribution (V_d), which describes the extent of distribution of the drug into tissue compartments. Lipophilic drugs are able to traverse biological membranes and enter most of

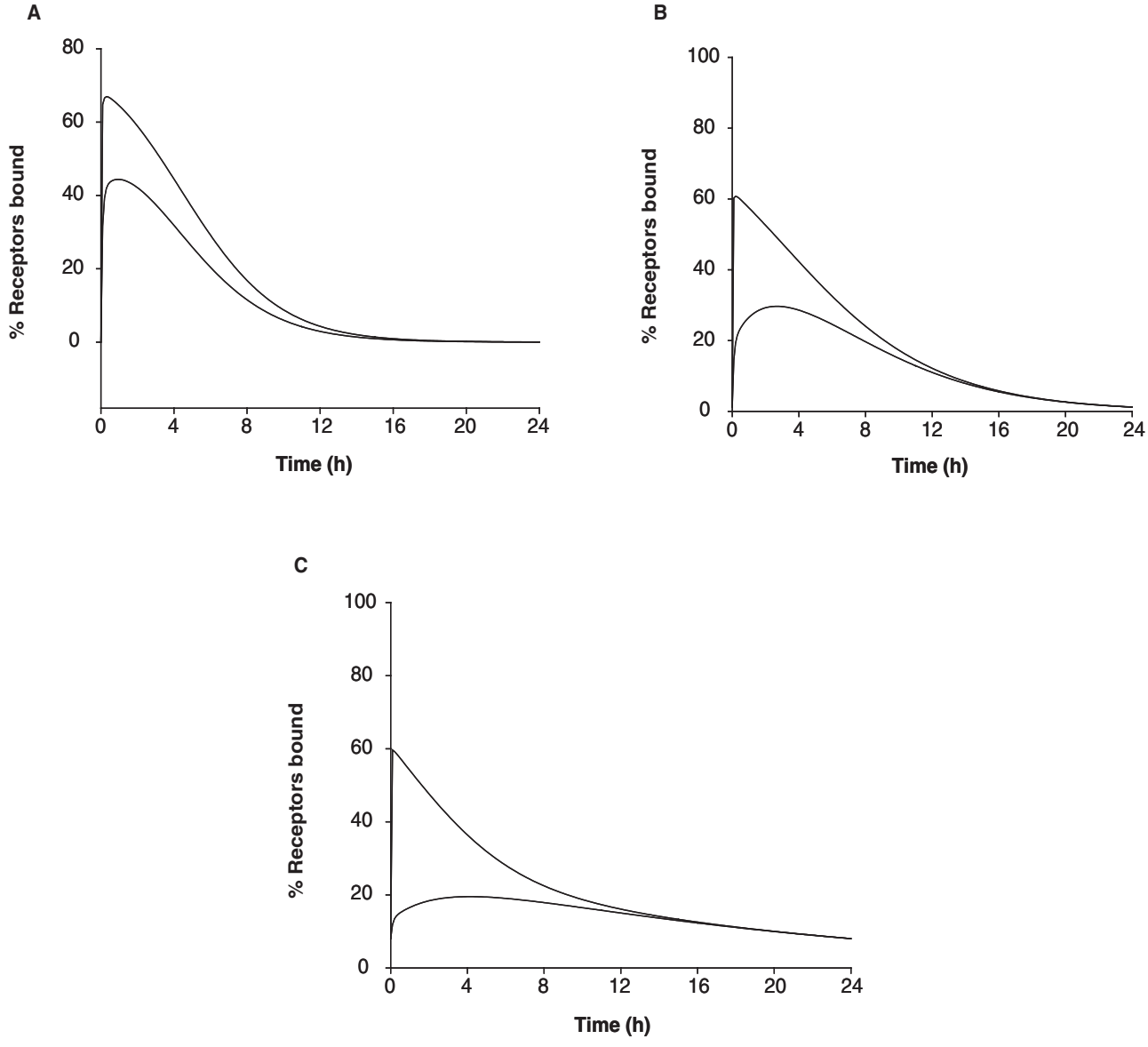

Figure 6. The effect of V_d on pulmonary (upper line) and systemic (lower line) receptor occupancies. The simulations show the effect of increasing V_d (100, 300 and 500 l for **A**, **B** and **C**, respectively) on pulmonary targeting. All other factors are unchanged.
V_d: Volume of distribution.

the tissue compartments (volume of the tissue compartment [V_t]). The V_d can be calculated by knowing the fraction of drug unbound in plasma and in tissue (f_u and f_{uT}, respectively), as well as the volume of the plasma (V_p), using the following relationship:

$$V_d = V_p + V_t \frac{f_u}{f_{uT}}$$

The higher the tissue binding compared with the plasma protein binding, the larger the V_d and, therefore, more drug will be in the peripheral compartment. Although this will cause the drug to have a greater half-life, it will not change the degree of pulmonary selectivity, as shown in **Figure 6**. Thus, inhalation drugs with a prolonged half-life do not hamper safety, as long as the half-life is due to extensive tissue binding and not a decrease in clearance.

At present, more lipophilic drugs are in development that show both increased plasma protein and tissue binding and, as a result, small f_u and f_{uT} values. There are, however, no significant increases in V_d because both f_u and f_{uT} are increased. Due to the decrease in the overall free fraction of

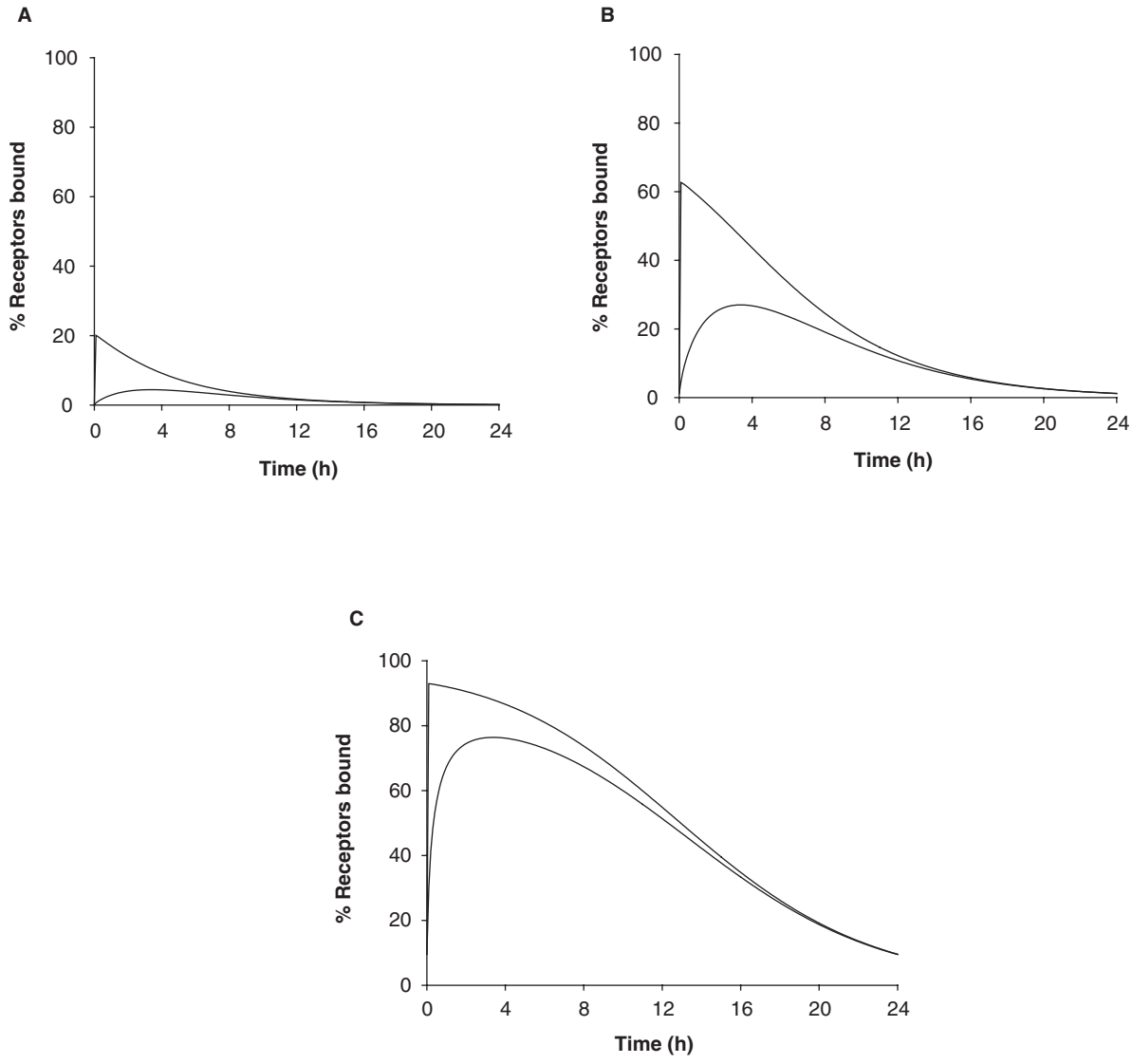

Figure 7. The effect of inhaled dose on pulmonary (upper line) and systemic (lower line) receptor occupancies. The inhaled dose was changed for each simulation (to 40, 400 and 4000 µg for **A**, **B** and **C**, respectively) and all other parameters were kept the same.

drug, the local and systemic effects will be smaller than that of an equivalent drug with an equivalent volume of distribution, but with lower plasma protein and tissue binding. The drug with the higher degree of binding will show reduced systemic side effects and most likely decreased pulmonary effects at a given concentration [19]. Systemic side effects are regarded as 'hard' parameters in clinical studies because concentration–response relationships are easier to obtain, whereas pulmonary effects are generally 'soft' parameters because concentration–effect relationships are more difficult to detect. Thus, such high-binding drugs at equivalent doses may produce lower systemic effects, whereas clinical studies may show equivalent efficacy in the antiasthmatic effects. As a result, a drug with high plasma/tissue binding may suggest a higher safety profile.

3.3 Pulmonary deposition efficiency

The therapeutic response of an inhaled drug is a function of the dose that is deposited at the site of action in the lung [38-40]. The amount of drug that reaches the lung, and which region of the lung (central or peripheral), is influenced by factors such as the device type, the aerodynamic diameter of the drug particles, the breathing pattern of the patient and the nature of the airway obstruction [41]. The optimal therapeutic response is found with inhaled drugs in which the mass median aerodynamic diameter is 0.5 – 5 µm. Techniques employed to evaluate lung deposition are generally based on *in vivo* radiographic imaging studies [42,43]. These methods include γ-scintography, single photon emission tomography and positron emission tomography. These applications are able to provide specific information

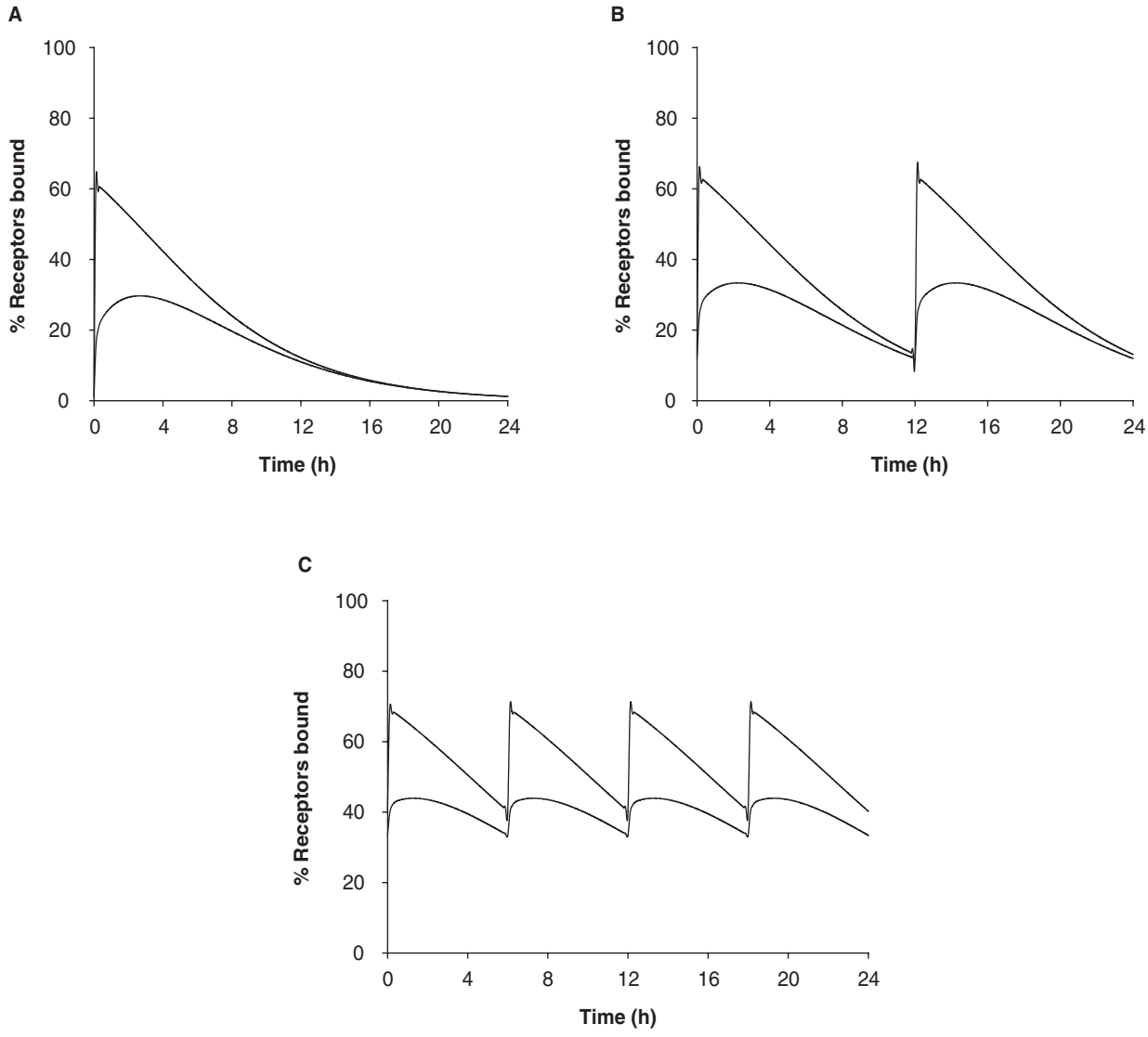

Figure 8. The effect of dosing regimen at steady state on pulmonary (upper line) and systemic (lower line) receptor occupancies. The simulations were performed for an inhaled drug administered at 800 µg/day, 400 µg b.i.d. and 200 µg four times a day for **A**, **B** and **C**, respectively. All other relevant factors remained constant throughout the simulation process.

regarding the amount, and location of pulmonary deposition. The deposition of drug into the lungs can vary depending on the type of delivery device used for therapy. It is clear that a higher degree of pulmonary targeting will be observed from a delivery device that can achieve more efficient pulmonary deposition. More efficient pulmonary deposition would clearly indicate that more drug will be delivered to the desired site of action and less would be available to be absorbed from the GI tract. In addition, with increased pulmonary delivery, a smaller overall dose will be necessary and a reduction of systemic side effects may be observed for drugs with a distinct oral bioavailability. Recently, there have been many improvements in pulmonary delivery technology, which have increased pulmonary deposition efficiencies by ≤ 50% [44,45] and shown more peripheral deposition. It will be interesting to learn more about the relationship between the region of pulmonary deposition and clinical efficacy. Improved pulmonary deposition is especially important for drugs with a high oral bioavailability because an increase in pulmonary deposition will cause a reduction in the amount of drug that is available for oral absorption [21]. Conversely, for a drug with low oral bioavailability, it is not important to have high pulmonary deposition because any drug that enters the GI tract will not be able to exert any systemic side effect. In this case, the dose of the inhaled drug should be reduced, otherwise increased pulmonary deposition will result in increased systemic side effects; because more drug will enter the systemic circulation through pulmonary absorption when a more efficient inhaler is used without dose adjustments.

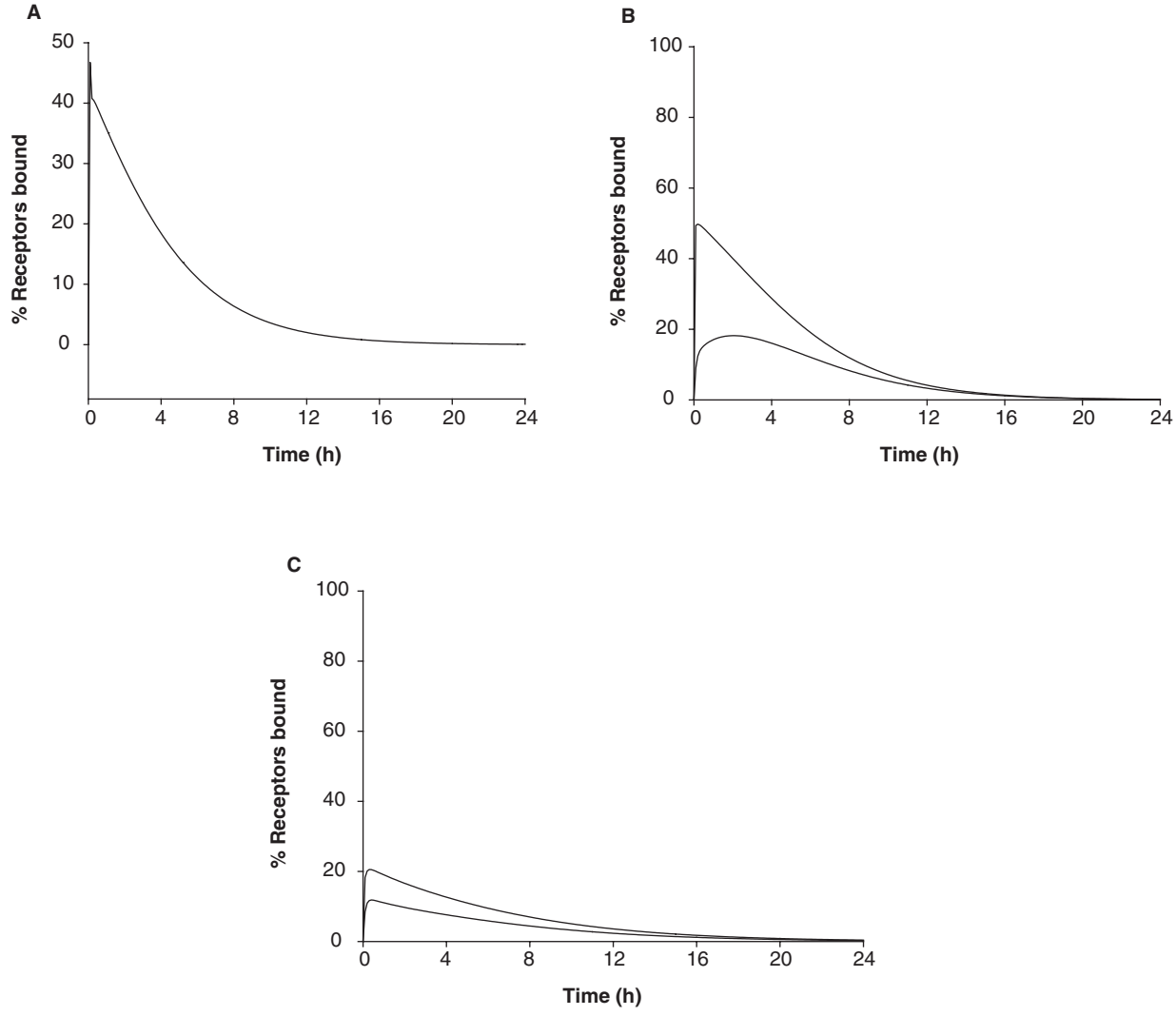

Figure 9. The effect of dissolution rate in the lungs on pulmonary (upper line) and systemic (lower line) receptor occupancies with the assumption that once the drug is dissolved it will enter the systemic circulation. The dissolution rate was the only parameter changed during the simulations: $t_{1/2}$ = 0, 3 and 24 h in **A**, **B** and **C**, respectively.
$t_{1/2}$: Half-life.

3.4 Inhaled dose/number of doses

Dosage regimens of inhaled drugs for asthma patients can vary according to the severity of their condition, where lower doses are given to patients with mild asthma and higher doses prescribed for patients with more severe asthma. As shown in **Figure** 7 pulmonary targeting can change as a function of the total dose administered. At low doses, most of the pulmonary and systemic receptors remain unoccupied, leading to smaller pulmonary and systemic effects. As the inhaled dose is increased, the differences in the observed pulmonary and systemic effects are more visible. At the highest dose, practically all of the systemic and pulmonary receptors are bound, thus leading to a loss of pulmonary targeting. The simulations show that there is an optimal dose in which maximum pulmonary targeting can be achieved, and that giving high doses of inhaled drug can lead, not only to higher pulmonary effect, but also higher systemic effects. This can be useful in terms of implementing dosage regimens and obtaining maximal clinical responses.

Another factor that must be considered for pulmonary selectivity is the number of doses. As shown in **Figure 8**, the degree of pulmonary targeting is enhanced with an increase in the number of daily doses. This is a result of prolonging the pulmonary drug exposure time and by increasing the pulmonary drug levels. Therefore, increasing the frequency of dosing will augment the therapeutic effect, especially for inhaled drugs that are rapidly absorbed from the lung. This was shown in a clinical study, which found that repeated dosing led to increased antiasthmatic effects of budesonide [46]. With an increase in the number of doses, there will also be a slight increase in systemic side effects;

however, this will be compensated for by a more dramatic increase in pulmonary effects. This may lead to an increase in pulmonary selectivity, a reduction in the overall dose and, consequently, an increase in safety (reduced systemic effects).

Although increasing the number of doses may show increased pulmonary selectivity, it is known that this may not be desirable to the patient and may lead to decreased patient adherence to therapy. Thus, other methods of prolonging the exposure time of the drug to the lungs should be examined.

3.5 Pulmonary residence time

Current formulations of inhaled drug mainly consist of drug either in a liquid suspension or as a dry powder. In order for the drug to exert its pharmacological effect in the lungs, it must first come into contact with the inside surface of the airways. It must then dissolve into the fluid lining where it will diffuse to the site of action and interact with the drug receptors and induce their effect. This will be followed by absorption of the drug into the systemic circulation. Due to the presence of thin membranes, a high number of pores and the presence of a sink condition in the lungs due to the high rate of pulmonary blood flow, the absorption of inhaled drugs is relatively fast across the pulmonary membrane [19]. Thus, the inhaled drug that dissolves will exit the lungs in a short amount of time, making the pulmonary residence time in the lung very short. It follows, therefore, that the dissolution rate of inhaled drug particles is a primary determinant of residence time in the lungs. The PK/PD model was used to simulate what changes would take place in pulmonary targeting when the dissolution rate of the drug in the lungs was modified (**Figure 9**).

Figure 9 shows how a rapid dissolution rate of the drug in the lungs leads to a decrease in pulmonary selectivity because it will be absorbed quickly into the systemic circulation and not have any exposure to the lung. If the dissolution rate in the lung is decreased, the drug concentrations in the lung will increase over time when compared with drug in the systemic circulation. This would indicate sustained drug release in the lungs to be beneficial; however, considerations must be made for drug that dissolves too slowly. Drug particles that are in the upper regions of the lung are subject to mucociliary clearance. This will result in a loss of efficacy and pulmonary targeting. From these simulations, it is evident that an optimal inhaled drug formulation should have the appropriate dissolution rate in order to obtain maximal pulmonary targeting.

Strategies to prolong the residence time of drug in the lung by modifying the physicochemical properties of the drug have been explored. They include the use of liposomes [47-49], microspheres [50-52] and ultrathin coatings [53], or lipophilic drugs with slow dissolution characteristics. Other approaches have utilised biological phenomena for prolonging the pulmonary residence time. Long-acting β_2-adrenergic drugs have strong binding affinities to areas different to nonreceptor pocket areas. These exo-sites keep the drug in the lung [54]. Glucocorticosteroids with free 21-OH groups, such as budesonide, form ester conjugates in the lung that can act as intracellular depots [55-57]. Such steroids enter pulmonary cells and a fraction will be converted within the cells into lipophilic esters. These ester conjugates cannot move across pulmonary membranes and are thus trapped in the lungs. The ester conjugates are then slowly broken down into free drug by esterases, which cause a sustained intracellular drug presence. This results in an increased pulmonary residence time and an increase in pulmonary targeting. In addition, this esterification mechanism may explain why drugs such as budesonide can be dosed once a day in certain patient populations. The relatively low esterification efficiency may also suggest that new drug entities with more efficient ester formation could be identified.

Depot formulation would lead to another advantage in asthma therapy. One of the major problems in the treatment of pulmonary diseases is associated with compliance, especially for drugs that do not show an immediate improvement in symptoms, such as glucocorticoids. Drug formulations that would allow a reduction in the frequency of administration (e.g., once-daily inhalation) would be likely to improve compliance. Thus, formulations or drugs with optimised pulmonary residence time would also lead to improved compliance. However, other approaches, such as dose-counting devices, are also important strategies used to improve and control compliance.

4 . Conclusion

Inhaled drug delivery will remain the cornerstone of asthma therapy for years to come. This review article has summarised the PD and especially the PK factors that play an important role in pulmonary targeting. Properties such as high clearance, low oral bioavailability and the factors contributing to a high pulmonary residence time are all significant in terms of achieving optimal pulmonary targeting.

5 . Expert opinion

Evaluating the landscape of commercially available last-generation glucocorticoids, such as budesonide and fluticasone propionate, and β_2-adrenergic drugs, such as formoterol and salmeterol, suggests that from an efficacy and safety standpoint these drugs already have a very high standard. Further developments in this area will, therefore, result in small improvements and will not represent quantum leaps.

Future advances in pulmonary drug delivery for glucocorticoids will be multi-facial. Developments will try to identify drugs or drug delivery systems with improved pulmonary PKs (longer pulmonary residence time). Further improvement in pulmonary deposition efficiency will run parallel with the removal of chlorofluorocarbon technology. Information on what specific regions of the lung need to be targeted to increase efficacy will result in more specific delivery to certain pulmonary regions (central and/or peripheral). Changes in the delivery devices (dry powder inhaler, nebuliser, MDI)

will incorporate technology that will increase patient compliance through either mechanical or electronic approaches. An improved understanding of the mode of action of glucocorticoids will result in a further dissociation between desired effects and side effects (e.g., transactivation versus transrepression). The identified synergism of co-administered glucocorticoids and long-acting β_2-adrenergic drugs [8,58] will result in more research in this area, and a better understanding of these interactions may lead to more improved treatment strategies.

Although drug companies will also focus on the identification of alternative therapeutic approaches with desirable oral administration routes, inhaled glucocorticoids will remain the cornerstone of asthma therapy as they attack the pathophysiology of the disease at a central crossroad. A gradual improvement of inhaled asthma therapy with improved efficacy and safety will also be possible. One should, however, be warned of the danger that new developments may be driven more by marketing and less by science.

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