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Pharmaceutical Solvents for Pulmonary Drug Delivery

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Introduction

It must first be recognized that formulating compounds and delivering them as aerosols is complex. Not only does it involve the formulation of a stable solution or suspension in a medium (propellant) that is not as well characterized as other systems, but the resultant system is also subject to performance limitations. In order to efficiently reach the lung, the formulation must be atomized into particles having aerodynamic sizes between approximately 1 and 5 microns. Due to these particle size constraints, as well as inhalation toxicology concerns, the range of possible excipients to choose from during the formulation phase is substantially reduced. Additionally, limiting the concentration of excipients in a formulation is crucial for maintaining adequate aerosol performance. Thus, given the complexity of this relationship, formulating aerosols is a challenging endeavor.

Although complex, the successful formulation of drugs for pulmonary delivery provides a valuable therapeutic route. Upon introduction of the metered dose inhaler (MDI), medical treatment of lung diseases changed significantly. Since that time, MDIs have become the most effective means of controlling symptoms of lung diseases such as asthma and chronic obstructive pulmonary disorder (COPD). More recently, formulation modifications were merited when chlorofluorocarbon (CFC) propellants were linked to the depletion of the ozone layer (Molina and Rowland, 1974). With the successful transition to new propellant systems, MDIs are still well accepted and highly utilized by patients across the globe today. Looking forward, the effectiveness, ease of use, and relatively low cost of aerosol preparations in combination with modifications in delivery technology and formulation sciences, will likely expand the treatment of diseases

previously untreated via the respiratory tract. The approval of inhaled insulin in early 2006 is a paramount example of the potential for delivering proteins and peptides via the pulmonary route.

A Brief History: From CFCs to HFAs

The first metered dose inhaler, Medihaler Epi™ was introduced in 1956 by Riker Laboratories (3M Pharmaceuticals) for the management of asthma and COPD. The delivery device has been well accepted since that time, as evidenced by the annual production of over a half-billion units (McDonald and Martin, 2000). Since the introduction of the MDI, β-adrenergic agonists, anticholinergics, corticosteroids, and cromolyn compounds have been the staple of management for the commonly occurring lung diseases, asthma and COPD.

Historically, the MDIs have utilized CFC propellants to provide the energy for atomizing the formulation upon actuation. Some characteristics that made CFC propellants attractive for pharmaceutical aerosols were their limited toxicity, inertness and suitable vapor pressures (Smyth, 2003). CFCs were not only readily used in MDIs, but were also highly utilized in a myriad of household aerosol sprays, air conditioners (as refrigerants), fire extinguishers, and also for industrial manufacturing of foams and insulations, including NASA's application of insulation to space shuttle rocket boosters (NASA, website). Despite the significant advances that CFC propellants enabled, they were found to be contributing to depletion of the ozone layer and to the greenhouse effect (Molina and Rowland, 1974).

Due to the environmental ramifications of CFC use, the Montreal Protocol was devised, and then ratified in 1989, initiating the phase-out of CFC propellants, including those used in MDIs (Figures 1a-c). As of 2002, the Montreal Protocol has been ratified by 183 countries (UN Environmental Program, 1996). However, because pharmaceutical inhalers are considered life saving for many asthmatic and COPD patients, they were exempted from the protocol pending availability of suitable alternatives (FDA, 21CFR(2), 2002).

As a result of the Montreal Protocol, significant research and resources were invested for the development of alternative non-CFC containing products, namely dry powder inhalers and nebulized solutions, in addition to other suitable propellants to replace CFCs for use in MDIs. Two candidates for CFC replacement were identified, HFA 134a (Figure 1d) and HFA 227 (Figure 1e). These hydrofluoroalkanes lack the ozone depleting characteristics of their predecessors; however, they still contribute to the greenhouse effect, albeit to a lesser degree than their CFC counterparts, as displayed in Table 1 (Smith, 1995). Additionally, the half-life of these HFA propellants in the atmosphere is a fraction of that of the CFCs they would ultimately replace (McDonald and Martin, 2000).

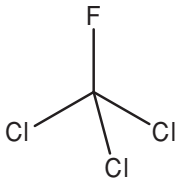

Figure 1a. CFC 11, trichlorofluoromethane.

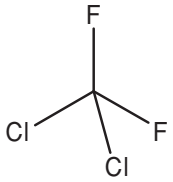

Figure 1b. CFC 12, dichlorodifluoromethane.

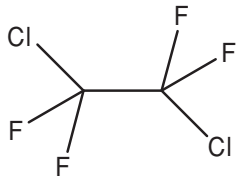

Figure 1c. CFC 114, 1,2-dichlorotetrafluoroethane.

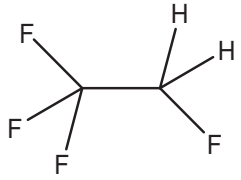

Figure 1d. HFA 134a, 1,1,1,2-tetrafluoroethane.

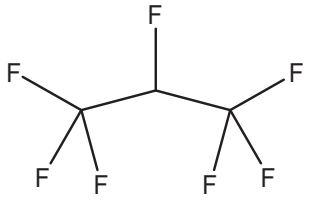

Figure 1e. HFA 227, 1,1,1,2,3,3,3-heptafluoropropane.

Choosing a Propellant: Characteristics of HFA 134a and 227

Several authors have described the physiochemical properties and differences observed between CFCs and HFAs (Smyth, 2003, Pischtiak et al., 2000, Vervaet and Byron, 1999, Tiwari et al., 1998). As Table 2 exhibits, the two HFA

Propellant	Ozone depletion potential*	Atmospheric life (years)	Global warming potential*
CFC 11	1	60	1
CFC 12	1	125	3
CFC 114	0.7	200	3.9
HFA 134a	0	16	0.3
HFA 227	0	33	0.7

Table 1. Environmental impact of pharmaceutical propellants.

* Relative to CFC 11. [7]

propellants that are currently utilized have boiling points and vapor pressures comparable to CFC 12 (dichlorodifluoromethane), the chief propellant used to obtain sufficient vapor pressure when used in blends (McDonald and Martin, 2000). However, HFA 134a and 227 do not display the same solvency characteristics of the CFCs (Vervaet and Byron, 1999). Presumably, this is due to the lack of polarizability of the fluorinated hydrocarbons as compared to the partially chloro-substituted CFCs (Smyth, 2003). This decrease in polarizability relative to CFC propellants could help explain some solubility differences of solutes in HFA based systems, despite their increased polarity over CFCs. Another major difference between the propellants is the hydrogen(s) on the HFAs, resulting in an increased dipole moment relative to CFC propellants which are completely chloro- and fluoro-substituted. As a result of this dipole, the highly electropositive hydrogen(s) appear to make the environment much less amenable to nonpolar solutes, while potentially enabling a degree of hydrogen bonding.

Although the above characteristics may begin to explain the difference in observed propellant-excipient/drug interactions, it is arguably academic, as CFC propellants are not a propellant option for future therapeutics. Thus, when formulating MDIs, there are only two propellants currently available, HFA 134a and HFA 227 (pictured in Figures 1d and 1e, respectively).

Propellant	Liquid density (g/ml)	Dipole moment (debye)	Boiling point (°C)	Vapor pressure (psig @ 20 °C)
CFC 11	1.49	0.46	23.7	−1.8
CFC 12	1.33	0.51	−29.8	67.6
CFC 114	1.47	0.50	3.6	11.9
HFA 134a	1.21	2.06	−26.3	68.4
HFA 227	1.41	0.93	−16.5	56

Table 2. Physiochemical properties of pharmaceutical propellants [10, 11].

Differences in the physical properties of HFAs, although minor, may warrant using 134a versus 227, or vice versa for a given formulation. Purity profiles of both propellants show a very low degree of impurity (both > 99.9% pure) (Solvay, 227, 134a Prod. Information), and do not significantly impact the choice of propellant. Compared to CFC propellants, both HFAs have relatively low boiling points (as seen in Table 2) which afford sufficient vapor pressure at lower temperatures without compromising efficiency (Stein and Stefely, 2003; Hoye et al., 2005). Additionally, they are completely miscible in one another and vapor pressure upon mixing behaves ideally, thus they may be blended in different proportions to obtain a specific vapor pressure or density (Williams et al., 1998). There is no toxicological advantage to either propellant, nor is there a degradation concern of one over the other, under relatively normal storage conditions (Solvay, 227, 134a Prod. Information). That said, some potential differences which may persuade a formulator mainly relate to chemical structure and resultant properties. HFA 227 has a $\log K_{ow}$ of 2.05 versus 1.06 for 134a, and as such, water has nearly four-fold increased solubility in HFA 134a versus 227 (2200 and 610 ppm, respectively). Of note, both HFA 134a and 227 have significantly greater water uptake as compared to the aforementioned CFC propellants (all ~120ppm), likely due to the relatively increased polarity (Solvay, 227, 134a Prod. Information). Thus, when formulating a suspension of a compound, physical stability as a function of water shall require addressing. Likewise, if in a solution formulation, the compound of interest is water labile, HFA 227 may offer advantages, though the formulation may still be susceptible to water migration. Williams and Hu (2000) confirmed these findings experimentally, though did not obtain the same magnitude of difference. They also showed that depending on the drug, emitted particle size could change, and likewise the fine particle fraction (fraction of aerosol less than 4.7 microns). Additionally, they indicated container lining and storage temperature for impacting increased water content.

Excipients for Metered Dose Inhalers

The Montreal Protocol, mandating the discontinuation of CFC propellants, gave the pharmaceutical industry a chance to reevaluate technical attributes of the MDI system. Due to the different physical characteristics of the propellants, excipients previously used in CFC based systems do not behave the same in HFA propellants and therefore also needed to be reinvestigated.

Surfactants were one excipient family which required reevaluation in HFAs. Surfactants are used in MDIs for several reasons: seal lubrication, emulsification, dispersion, solubilization, and as a preservative. Surfactants used in CFC formulations such as lecithin, sorbitan trioleate, soya lecithin, and oleic acid are highly soluble in CFC propellants (particularly CFC 11), however in HFA propellants, the solubility of these surfactants is relatively poor. Several authors point out that surfactant polarity, indicated by their respective hydrophilic-lipophilic balance (HLB) correlates with the incompatibility of the aforementioned surfactants

Excipient[a]	Product	Function	Maximum approved concentration[b]
Sorbitan trioleate (Span 85)	Aerobid, Alupent, Intal, Maxair, Tilade	Surfactant Dispersion Suspension Solubilization agent	0.069%
Soya lecithin	Atrovent, Combivent	Dispersion	0.28%
Lecithin	Flovent, Serevent	Dispersion Solubilization	0.00025%
Oleic acid	Beclovent, Proventil, Proventil HFA, Vanceril, Ventolin, Xopenex HFA	Dispersion Emulsification	0.267%
Cetylpyridinium chloride	Asthmahaler Mist, Bronkaid Mist	Preservative Surfactant	

Table 3. Commonly used surfactants in previously approved products.

[a]All excipient tables (3, 4, 5) were produced using US FDA Center for Drug Evaluation and Research Inactive Ingredient List for Approved Drug Products, updated 10/31/2005, along with product monographs for respective listed products.

[b]Maximum concentration in a product previously approved by the United States Food and Drug Administration.

in the more polar HFA environment (Vervaet and Byron, 1999; Ridder et al., 2005). Table 3 lists previously approved surfactants utilized in MDIs along with their maximum concentration approved by the United States Food and Drug Administration (U.S. FDA).

Co-solvents in metered dose inhalers were commonly used in CFC formulations to aid in drug solubilization. In HFA formulations, co-solvents continue this same function, but have additional benefits in the new systems, such as solubilization of other excipients. Vervaet and Byron discuss water solubility in the various propellants addressed here, where the addition of ethanol to the HFA system considerably increases the solubility of water (Vervaet and Byron, 1999). Likewise, ethanol was found to increase the solubility of several surfactants in HFA (Vervaet and Byron, 1999; Stein and Stefely, 2003). Suspension formulations using this technique (surfactant plus ethanol) must be made with caution however, as ethanol can also increase the solubility of the drug substance, potentially causing increased particle growth via Ostwald ripening. Nonetheless,

without the use of ethanol as a co-solvent, several currently accepted surfactants would be virtually unusable in HFA systems.

Dosing Efficiency

Although co-solvent use is a successful method of improving drug/excipient solubilization in aerosol systems, there are limitations to this technique. Simply increasing the drug concentration in a formulation does not guarantee an increase in the total amount of respirable drug delivered.

The addition of non- or semi-volatile excipients (including the active drug substance) has multiple effects on the delivery process. These systems will have a reduced vapor pressure, which affect the atomization of the formulation. All else equal, there is less force generating aerosol droplets of a given surface tension, viscosity, etc., thus larger initial droplets. Second and potentially more important, these larger (and fewer) aerosol droplets take longer to dry as the total surface area is decreased, compared to a higher number of smaller aerosolized droplets (analogous to micronizing solid drug particles to increase solubility). The result of these two dynamic processes, albeit occurring simultaneously, results in larger final particle diameter. An increased proportion of larger particles directly correlates to a decrease in respirable fraction/mass (decreased fine particle fraction/mass), thus decreased efficiency (Stein and Myrdal, 2006).

A prime example of this relationship was obtained from Gupta et al. (2003) where a linear increase in the solubility of beclomethasone dipropionate was observed with an increase in ethanol concentration from 0 to 20% (Gupta et al., 2003). Unfortunately, respirable fraction displayed an accompanying decrease (Myrdal et al., 2004a; Mogalian et al., 2005). Examining the sum of this relationship reveals diminishing increases in respirable deposition once exceeding 10% ethanol in the system (see Figure 2). Therefore, when increasing solubility of a compound via co-solvent (or other excipients) to achieve an appropriate dose or dose per actuation, delivery of the formulation may be simultaneously compromised, thus limited net gain is achieved. In some instances however, this relationship could be advantageous. If formulating an aerosol that displays a mass median aerodynamic diameter (MMAD) smaller than desired, as in the case of dilute (low dose) solution formulations, addition of a less volatile excipient such as water or propylene glycol, could help increase the particle size to a more desirable range of aerodynamic diameter.

Table 4 lists non-surfactant excipients that have been previously approved for use in MDIs by the U.S. FDA. The maximum concentration listed in Table 4 (and other related tables) was obtained from this source; however, the excipients in given products were obtained from their respective drug monographs. Given the independent sources of this information, it is impossible to determine if the cited concentration correlates to a particular product. Citing ethanol as an example, note that although the maximum approved concentration is 34.5%, it would greatly decrease the performance of a MDI, and likely no newer formulation

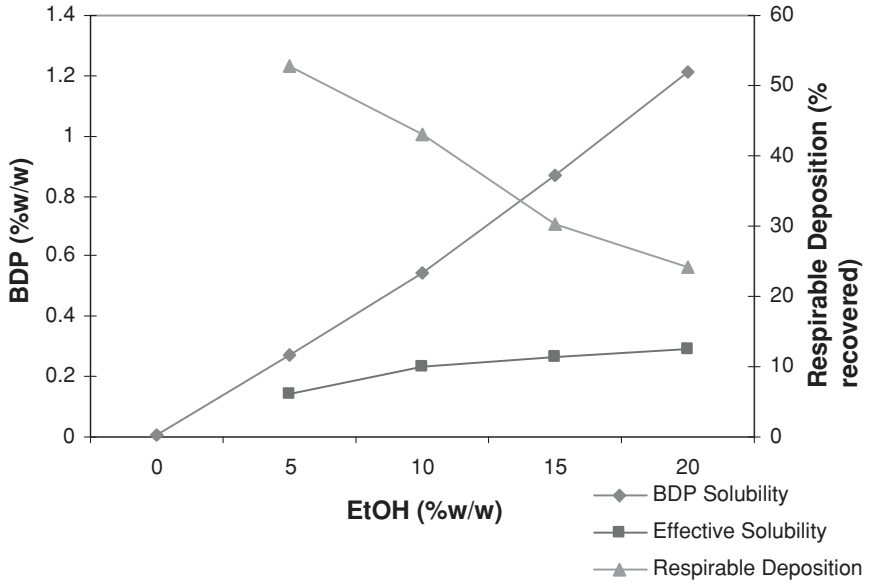

Figure 2. Gupta et al. [18] shows a linear increase in drug solubility with the addition of ethanol; however, there is an accompanying decrease in aerosol performance. Due to decreased efficiency, limited gains in respirable mass are observed when adding more than 10% ethanol (BDP = beclomethasone dipropionate).

would contain ethanol in that quantity. More typically, ethanol concentrations from 1-20% w/w are found in the literature.

Considerations for Nebulized Solutions

In formulating solutions for nebulization, more common techniques are available for solubilizing compounds. Unlike MDIs, nebulization solutions are aerosolized via an external energy source (ultrasonic or jet spray) in place of propellants. Thus, solutions for nebulization can be formulated as routine aqueous systems with additional considerations being made for the pulmonary toxicity of the excipients, volatility (with regard to final particle size), and flavor. Citric acid, sodium citrate, and saccharin sodium are three flavoring agents which have been used in nebulization solutions, the former two of these also acting as buffers to control pH within the formulation.

In addition to the buffers previously mentioned, other agents have also been employed to adjust the pH of nebulization solutions for drug stability and/or solubility reasons (Steckel et al., 2003). These agents include hydrochloric acid, sulfuric acid, and sodium hydroxide, and all have been used in marketed products, as seen in Table 5.

Microbial studies in MDIs showed that CFC propellant blends tended to be bactericidal against the commonly occurring bacterial contaminant *Staphylococcus aureus*. The same was found to be true for HFA 134a, however

Excipient[a]	**Product**	**Function**	**Maximum approved concentration**[b]
Ethanol/ Dehydrated Alcohol/ Alcohol	Azmacort, Isuprel, Primatene Mist, Tornalate, Qvar, Atrovent HFA, Proventil HFA, Xopenex HFA, Aerospan HFA, Alvesco	Co-solvent	34.5%
Water	Atrovent HFA	Co-solvent	
Menthol	Aerobid, Tornalate	Flavoring agent	0.05%
Saccharin sodium		Flavoring agent	0.045%
Saccharin	Tornalate	Flavoring agent	0.112%
Citric acid (anhydrous)	Atrovent HFA	Flavoring agent	0.00022%
Hydrochloric acid		pH adjustment	1.72%
Nitric acid		pH adjustment	1.67%
Ascorbic acid	Primatene Mist, Isuprel, Tornalate	Antioxidant	1.02%

Table 4. Common co-solvents and miscellaneous excipients in previously approved products.

[a]All excipient tables (3, 4, 5) were produced using US FDA Center for Drug Evaluation and Research Inactive Ingredient List for Approved Drug Products, updated 10/31/2005, along with product monographs for respective listed products.

[b]Maximum concentration in a product previously approved by the United States Food and Drug Administration.

HFA 227 was found to be bacteriostatic, which is at least sufficient to stop proliferation of *S. aureus* in the MDIs (McDonald and Martin, 2000). However, for nebulization solutions, propellants are not used and thus antimicrobial properties of these propellants do not apply; sterility must therefore be obtained by other measures. Table 5 displays several antimicrobial preservatives used in nebulization solution.

Excipient[a]	**Product**	**Function**	**Maximum approved concentration**[b]
Alcohol (ethanol)	Tornalate	Co-solvent	25%
Glycerin	Isuprel	Co-solvent Humectant Preservative Tonicity agent	7.3%
Propylene glycol	Tornalate	Co-solvent Preservative	25%
Methylparaben		Preservative	0.07%
Propylparaben		Preservative	0.037%
Chlorobutanol	Isuprel	Preservative	0.5%
Sodium meta bisulfite	Isuprel	Preservative	1%
Sodium bisulfite		Preservative	0.32%
Sodium sulfite		Preservative	0.1%
Sodium sulfate (anhydrous)		Tonicity agent	0.025%
Thymol		Preservative	0.01%
Benzalkonium chloride	Alupent, Proventil, Ventolin	Preservative Wetting agent Solubilizing agent	20%
Sodium chloride	Airet, Proventil, Isuprel, Xopenex, Atrovent, Duovent	Tonicity	3.16%
Sodium citrate/ Citric acid	Airet, Isuprel, Tornalate	Buffering agent Chelating agent Flavoring agent	0.6%/0.44%
Edetate sodium/ Edetate disodium	Airet, Alupent, Atrovent	Chelating agent	0.02%/0.03%

Excipient[a]	Product	Function	Maximum approved concentration[b]
Saccharin sodium		Flavoring agent	
Hydrochloric acid	Airet, Atrovent, Duovent	pH adjustment	3.5%
Sulfuric acid	Proventil, Ventolin, Xopenex	pH adjustment	12.5%
Sodium hydroxide	Tornalate	pH adjustment	8%
Ascorbic acid		Antioxidant	1.02%
Water			

Table 5. Previously approved excipients for inhaled solutions for nebulization.

[a]All excipient tables (3, 4, 5) were produced using US FDA Center for Drug Evaluation and Research Inactive Ingredient List for Approved Drug Products, updated 10/31/2005, along with product monographs for respective listed products.

[b]Maximum concentration in a product previously approved by the United States Food and Drug Administration.

Fortunately, many of the frequently used antimicrobial excipients are also used to enhance solubility. Glycerin and propylene glycol, for example, are both commonly used co-solvents but also exert antimicrobial properties through increased osmotic pressure. Similarly, benzalkonium chloride is a cationic surfactant that is commonly used as a wetting agent, emulsifying agent, as well as an antimicrobial. It exhibits antimicrobial effects through surface activity and is most effective against gram positive bacteria such as *S. aureus* via interaction with the cell wall. However, because it is a quaternary ammonium compound, it may not be compatible for use with coexisting anionic species, whether they be the drug itself, or other excipients in the formulation (Sigma-Aldrich, Prod. Information).

Novel Solubilization, Suspension, and Delivery Techniques

With the change to HFA propellants, several pharmaceutical companies saw an incentive to develop formulations, while companies with established inhalation products sought to protect their business (Stein and Stefely, 2003). Regardless, research in the aerosol field is far from limited to updating MDIs. New biological targets are regularly being discovered, which gives rise to new therapies and, ultimately, new formulation challenges. This section will address some of the newer trends in inhalation drug therapy, and some of the challenges of formulation.

Recently, biologically active proteins and peptides have received a great deal of interest. Although promising, inhalation therapy with proteins and peptide drugs has proved to be difficult. Due to the larger molecular size of these therapeutic proteins, and the importance of sterics to their activity, the high stress of aerosolization has proven to be of significance (Mumenthaler et al., 1994).

Williams and Liu investigated the delivery of the protein bovine serum albumin (BSA) via MDI as a suspension, using HFA 134a and combinations of ethanol with different surfactants and were able to obtain >1mg BSA/g formulation with respirable fractions up to 50% (Williams and Liu, 1998). Myrdal et al. examined cyclosporine as a model peptide in a formulation containing HFA 134a or 227 and low amounts of ethanol (2004b). They were able to deliver 500 μg/actuation with adequate particle size (MMAD roughly 2μm) and respirable fraction, while also showing formulation stability over a two year period. Additionally, Taljanski et al. demonstrated success dosing aerosolized cyclosporine A in rats utilizing the surfactant Cremophor® EL (Taljanski et al., 1997). This micellar solution resulted in increased pulmonary bioavailability over the regular solution (ethanol co-solvent) and suspension (saline based) in the study, thereby supporting the use of Cremophor® EL as a permeability enhancer for this drug, though the solution was not delivered by MDI (Taljanski et al., 1997).

Another recently developed delivery technology includes the use of phospholipids in HFA MDI formulations. Dellamary et al. describe their method of formulating an HFA based suspension of phospholipids, water and drug, using lecithin as a stabilizing agent (Dellamary et al., 2000). This formulation technique was initially employed to contain suspensions of cromolyn sodium, albuterol sulfate, or formoterol fumarate, and was later successfully tested using human immune globulin (IgG) to initiate an immune response in mice, via the respiratory tract (Bot et al., 2000).

Sustained release of aerosolized drugs has been investigated to some degree. Several approaches have been considered, including, liposomes, microspheres, prodrug formation, cyclodextrins, and *in vivo* precipitation. Many of these excipients are thought to demonstrate sustained-release properties via the same mechanism by which they display solvency characteristics. Liposomes, microspheres, and cyclodextrins were hypothesized to display sustained-release characteristics via entrapment or complexation. Zeng et al. describes a liposomal inhalation formulation containing sodium cromoglycate, an anti-asthmatic drug, where blood samples showed detectable levels of drug in the blood at 25 hours with a maximum concentration (C_{max}) seven times less than the regular solution formulation. The same solution formulation also resulted in undetectable concentrations in half of the time that the liposomal formulation took to reach undetectability, suggesting some degree of sustained-release (Zeng et al., 1995). Cyclodextrin formulations had received interest after showing slowed absorption rates of albuterol through pulmonary epithelial tissue *in vitro* when complexing with hydroxypropyl-β-cyclodextrin (HP-β-CD) (Wall et al., 1994). However, Wall et al. found that rat models showed no sustained-release properties with the same formulation. A phenomenon which may account for this has been previously documented, in which cholesterol would disrupt a drug

complex and preferentially take the place of the drug, due to higher affinity of cholesterol for HP-β-CD (Frinjlink et al., 1991).

Conclusions

Pulmonary drug delivery has proven useful for decades due to its tremendous advantage in treating diseases of the lung. Recently, pulmonary drug delivery has benefited from advances in technological (device) design, enabling generation of consistent aerosol delivery while also more effectively controlling emitted particle size. A large impact has also taken place in aerosol drug formulation. Doing away with environmentally detrimental CFC propellants forced reformulation and, consequently, gave an opportunity to improve upon existing formulations. With this came an improved understanding of HFA propellants and how they interacted differently with excipients which were formerly well characterized.

Despite the success of reformulating previously marketed products, research still needs to be conducted evaluating the basic physical properties of HFA propellants for most efficient future application. This includes further evaluation of solubilization properties and prediction for use with both small and large molecule drugs, as well as newer excipients including novel co-solvents, surfactants, lipids, polymers, and cyclodextrins. Moreover, new biologically active targets or diseases previously untreated via the pulmonary route will lead to new drugs and inevitably additional formulation challenges.

List of Abbreviations

CFC.....chlorofluorocarbon
COPD.....chronic obstructive pulmonary disorder
HFA.....hydrofluoroalkane
MMAD.....mass median aerodynamic diameter
MDI.....metered dose inhaler

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