The use of PFAS as processing aids in inhaled medication

M Friel
Aer Beatha

Inhaler Devices

Aerosol Drug Delivery Devices

Metered Dose Inhalers (MDIs)

Dry Powder Inhalers (DPIs)

Jet Nebulizers

Inhaler Timeline

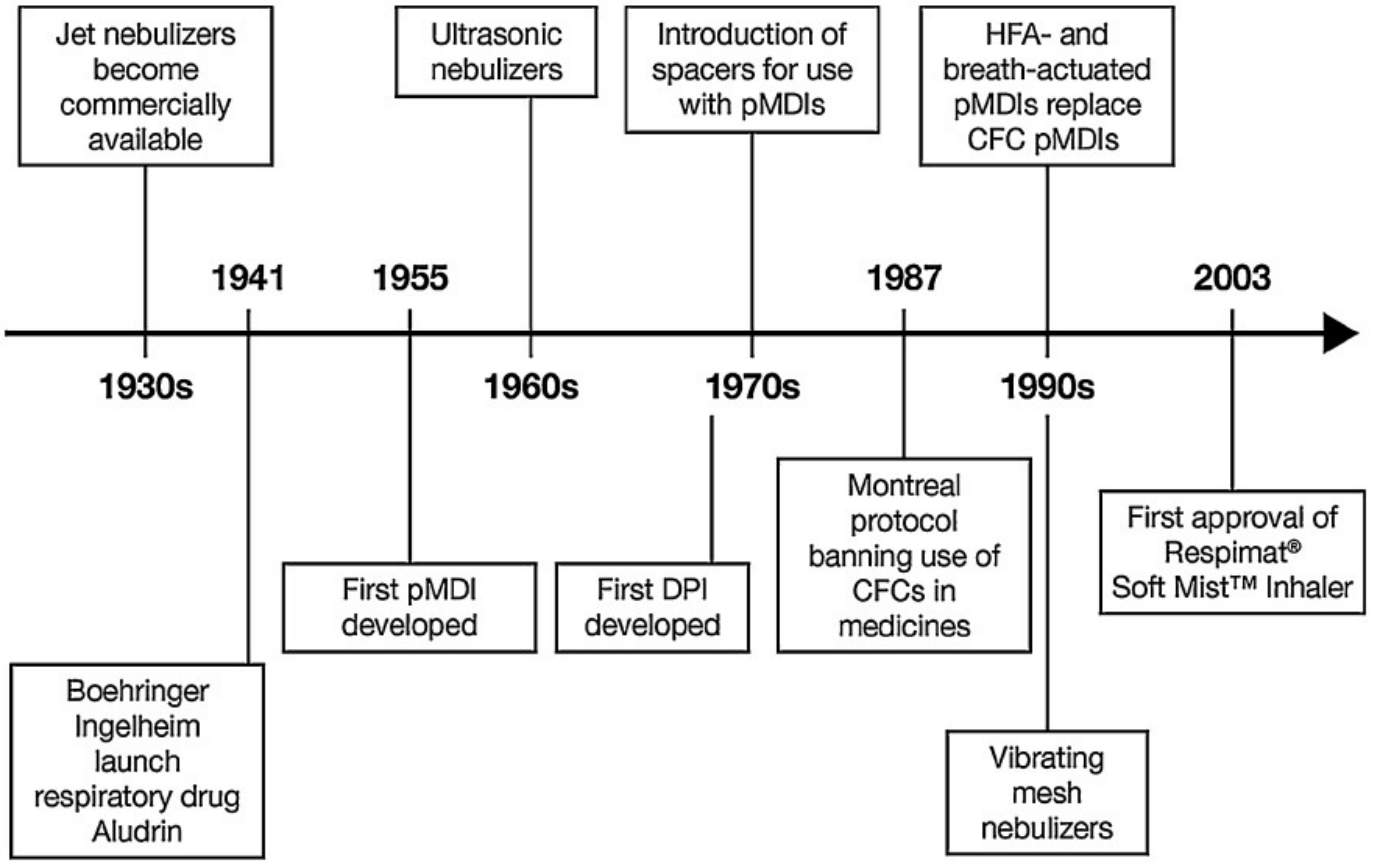
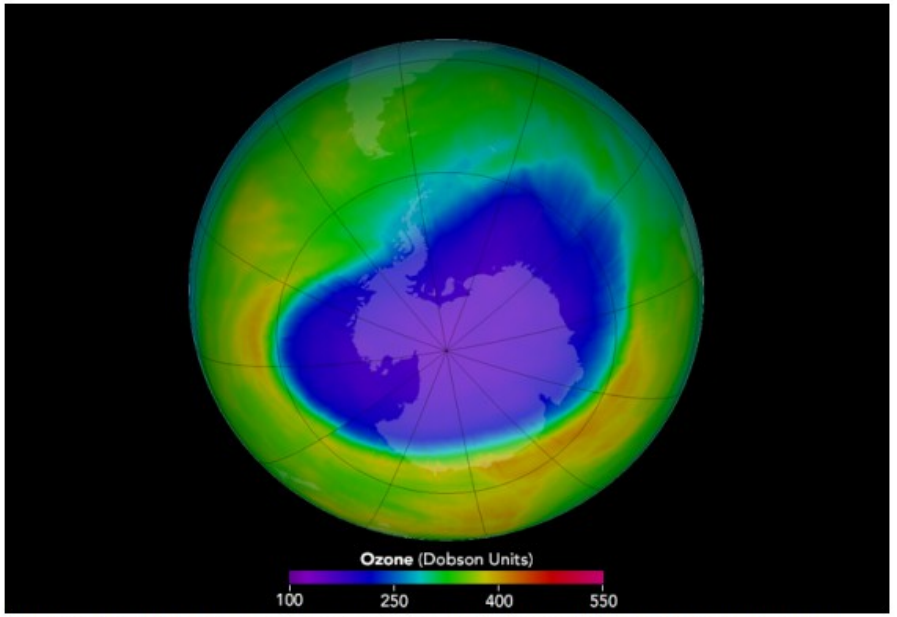


Fig. 1 Historical development of inhaler devices [6–16]. *CFC* chlorofluorocarbon, *DPI* dry powder inhaler, *HFA* hydrofluoroalkane, *pMDI* pressurized metered dose inhaler

Ozone Hole



NASA began measuring Earth's stratospheric ozone layer by satellite in 1979. By the time the Montreal Protocol went into effect in 1989, ozone concentrations (in Dobson units) had declined significantly over the Antarctic, enlarging the ozone hole. Ozone levels have since stabilized, but recovery is still decades away, according to NASA.

Courtesy Jesse Allen (2016), using Suomi NPP OMPS data provided courtesy of Colin Seftor (SSAI) and Aura OMI data provided courtesy of the Aura OMI science team. Suomi NPP is the result of a partnership between NASA, NOAA and the Department of Defense.

Atmos. Chem. Phys., 9, 2113–2128, 2009
www.atmos-chem-phys.net/9/2113/2009/

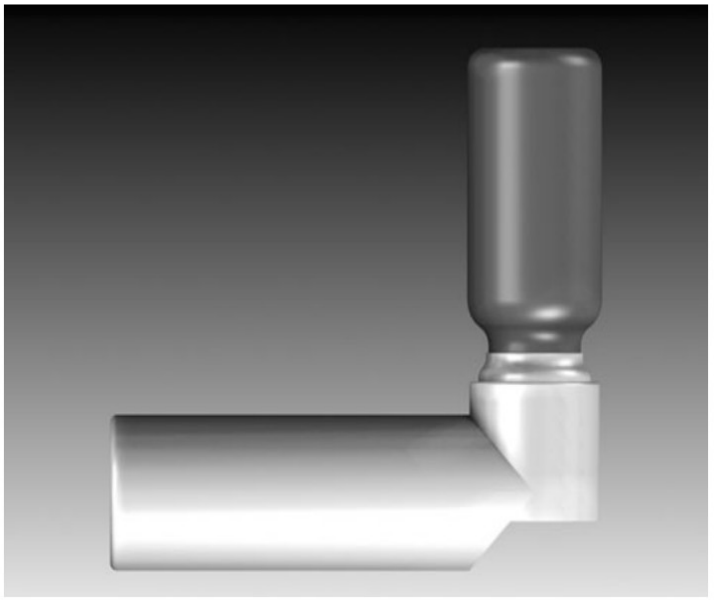
Atmospheric Chemistry and Physics

What would have happened to the ozone layer if chlorofluorocarbons (CFCs) had not been regulated?

P. A. Newman[1], L. D. Oman[2], A. R. Douglass[1], E. L. Fleming[3], S. M. Frith[3], M. M. Hurwitz[4], S. R. Kawa[1], C. H. Jackman[1], N. A. Krotkov[5], E. R. Nash[3], J. E. Nielsen[3], S. Pawson[1], R. S. Stolarski[1], and G. J. M. Velders[6]

https://www.acs.org/content/acs/en/education/whatischemistry/landmarks/cfcs-ozone.htm

Metered Dose Inhaler (MDI)

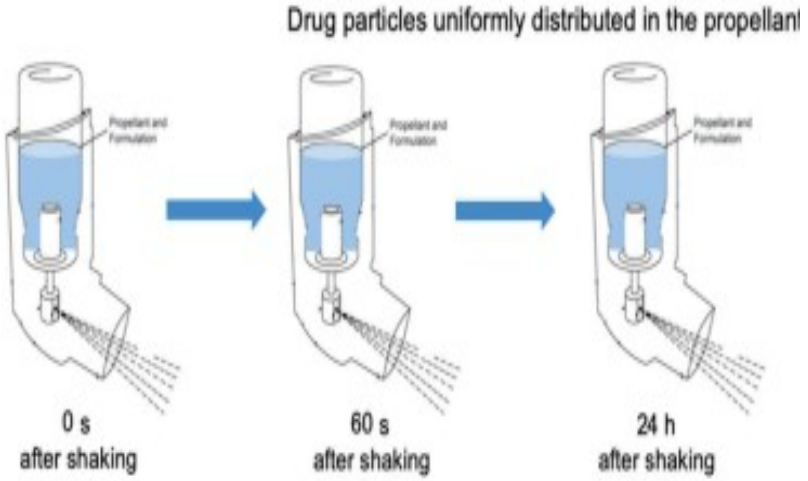


1956 CFC / adrenaline

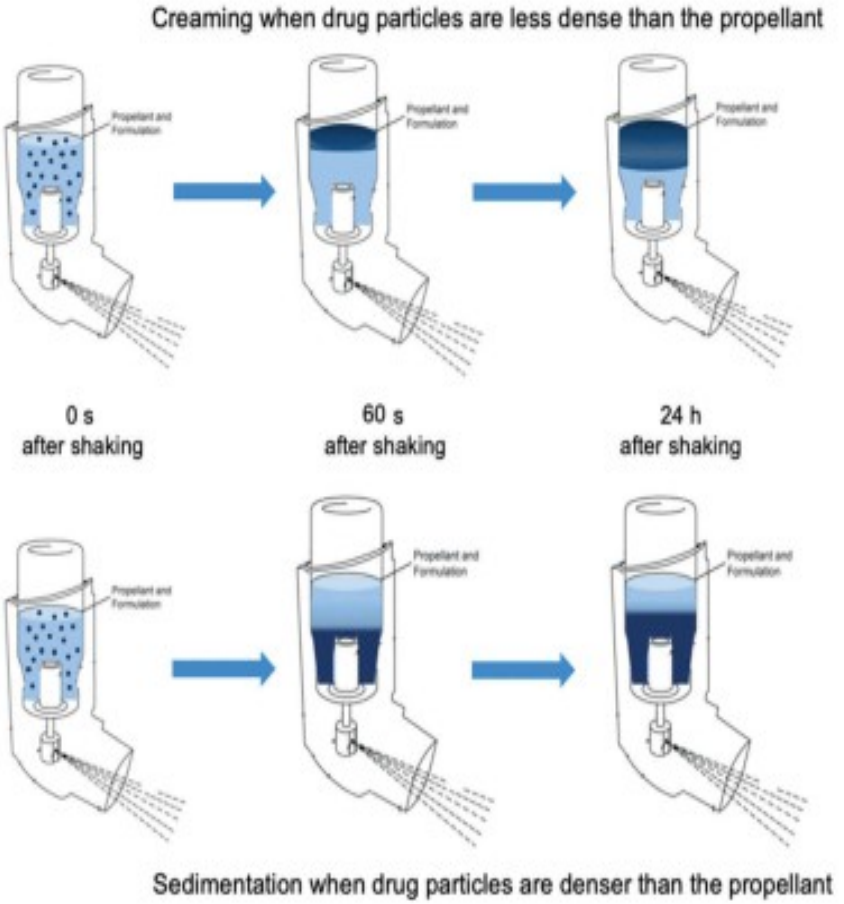
1999 HFC / salbutamol

Metered Dose Inhaler (MDI)

Solution



Suspension



EXPERT OPINION ON DRUG DELIVERY
https://doi.org/10.1080/17425247.2020.1767066

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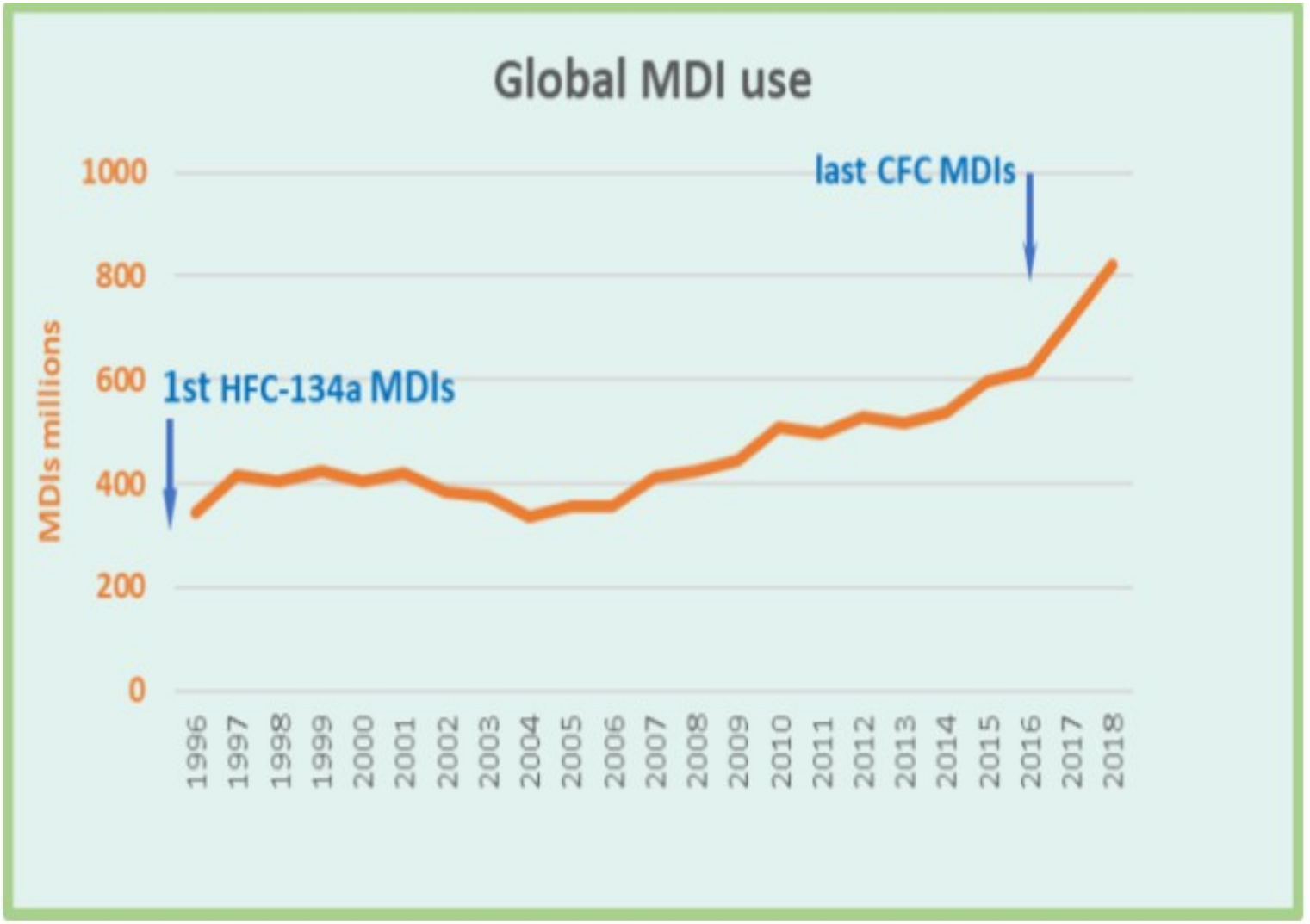
ORIGINAL RESEARCH

OPEN ACCESS Check for updates

Consequences of not-shaking and shake-fire delays on the emitted dose of some commercial solution and suspension pressurized metered dose inhalers

Veronica Chierici [a], Luca Cavalieri [b], Alessio Piraino [b], Davide Paleari [b], Eride Quarta [c], Fabio Sonvico [c], Andrea S Melani [d] and Francesca Buttini [c]

Volume of MDIs



*Medical and Chemical Technical Options Committee 2018 Assessment Report

Contribution to Global Warming

According to MCTOC* 2018, based on HFC manufacturing industry estimates, **approximately 800 million or more HFC MDIs (with average fill weight 13-14.5 g/MDI) are currently manufactured annually worldwide**, using approximately 11,500 tonnes HFCs in 2018. HFC-134a makes up the major proportion, with HFC-227ea accounting for about 8 percent. This corresponds to direct emissions with a climate impact of approximately 18,000 ktCO2-eq.

*Medical and Chemical Technical Options Committee 2018 Assessment Report

MDI propellant gases

	FC No.	Formula	B.Pt (°C)	S.G. (g/cc, 20°C)	ODP*	**GWP
CFC	11	$CFCl_3$	23.7	1.49	1	4660
CFC	12	CF_2Cl_2	-29.8	1.33	1	10800
HFA	134a	CF_3-CFH_2	-26.2	1.23	0	1300
HFA	227ea	CF_3-CFH-CF_3	-16.5	1.41	0	3350
HFA	152a	CF_2H-CH_3	-24.7	0.91	0	138
HFO	1234ez	CHF=CHCF3	-19	1.19	0	7

Properties of CFC/HFC Propellants

TABLE VI

The Commercial Properties of Major Chlorofluorocarbons and Alternative Compounds

CFC Number	Formula	Boiling Point °F	Boiling Point °C	Toxicology	Flammability	Comm. Mfg. Process	Worldwide Present or Potential Significant Commercial Applications: Aerosol	Refrig./A-c.	Blowing AG.	List Price (Dec-1981) $/Lb.	List Price (Dec-1981) $/Kg
11	CCl_3F	75	24	Low	None	Excellent	Excellent*	Excellent	Excellent	0.64	1.41
12	CCl_2F_2	-22	-30	Low	None	Excellent	Excellent*	Excellent	Excellent	0.74	1.63
13	$CClF_3$	-115	-82	Low	None	Good	None	Good	None	11.00c	24.30c
14	CF_4	-198	-128	Low	None	Fair	None	Fair	None	18.62c	41.06c
21	$CHCl_2F$	48	9	Toxic	None	Fair	None	—	Good	—	—
22	$CHClF_2$	-41	-40	Poss.v.wk.mutagen	None	Excellent	Good	Excellent	—	1.14	2.51
23	CHF_3	-116	-83	Low	None	Fair	None	Fair	—	13.46c	29.68c
31	CH_2ClF	16	9	Toxic	Yes	None	Fair	None	None	—	—
32	CH_2F_2	-61	-52	Low	Yes	None	None	None	None	—	—
113	$CCl_2F{\cdot}CClF_2$	118	48	Low	None	Excellent	Good*	Good	Good	0.79	1.74
114	$CClF_2{\cdot}CClF_2$	39	4	Low	None	Excellent	Excellent*	Excellent	Excellent	1.02	2.25
115	$CClF_2{\cdot}CF_3$	-38	-39	Low	None	Good	Good*	Good	Good	2.55tc	5.62tc
116	$CF_3{\cdot}CF_3$	-164	-109	Low	None	Fair	None	Fair	None	4.90c	10.80c
123	$CHCl_2{\cdot}CF_3$	82	28	Low	None	None	None	None	Fair	—	—
124	$CHClF{\cdot}CF_3$	12	-11	Low	None	None	None	Fair	Slight	—	—
125	$CHF_2{\cdot}CF_3$	-55	-48	Assumed low	None	None	None	Fair	None	—	—
132b	$CH_2Cl{\cdot}CClF_2$	116	47	Very incomplete	None	None	None	None	Poor	—	—
133a	$CH_2Cl{\cdot}CF_3$	45	7	Embryotoxic	None	None (USA)	None (USA)	None	Fair	—	—
134a	$CH_2F{\cdot}CF_3$	-16	-27	Very incomplete	None	None	None	None	Fair	—	—
141b	$CH_3{\cdot}CCl_2F$	90	32	Weak mutagen	Slight	Developmental	None	None	Good	—	—
142b	$CH_3{\cdot}CClF_2$	14	-10	Very weak mutagen	Slight	Good	Good	Fair	Good	1.75c	3.86c
143a	$CH_3{\cdot}CHF_3$	-54	-48	Incomplete	Moderate	None	None	Fair	None	—	—
152a	$CH_3{\cdot}CHF_2$	-13	-25	Low	Moderate	Excellent	Very Good	Good	Good	1.55	3.42
3110	C_4F_{10}	28	-2	Low	None	Discontinued	Fair	Good	None	—	—
C-318	C_4F_8	22	-6	Low	None	Fair	Fair	—	None	11.00tc	24.00tc
—	$(CHF_2)_2O$	28	-2	Very incomplete	None	Discontinued	Fair	—	—	12.00tc	26.00tc
—	$(CF_3)_2O$	-67	-55	Very Incomplete	None	Discontinued	Fair	—	—	—	—
—	$(CH_3)_2O$	-13	-25	Low	Yes	Very Good	Excellent	Poor	None	0.57	1.26
H-1301	$CBrF_3$	-72	-58	Low	None	Very Good	Specialized	Specialized	None	3.50c	7.72c
H-1211	$CBrClF_2$	28	-2	Low	None	Very Good	Specialized	Specialized	None	2.00c	4.40c
(LP Gases)	C_3H_8, etc.	—	—	Low	Yes!	Excellent	Excellent	None	None	0.22	0.48

*Banned in the U.S.A. for aerosols and partly banned or reduced in other countries. CFC-11 and 12 banned in Norway and Sweden.
Prices are for bulk (f.o.b.) unless noted by "c" = small cylinders (80 pound average net) or "tc" = ton cylinders. "e" represents an estimated price.
Some data may be slightly misleading due to brevity and those interested should pursue the available literature for more precise information.

The Aerosol Handbook M Johnson

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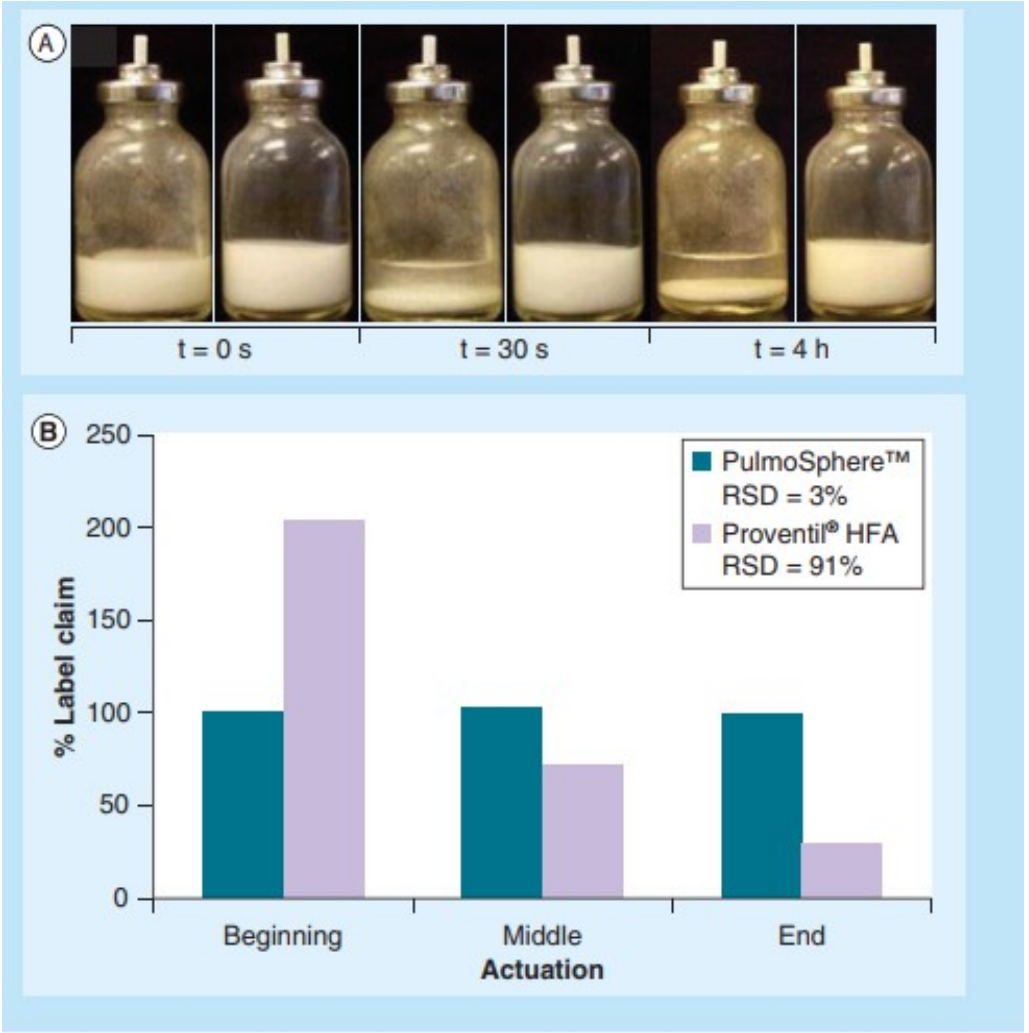

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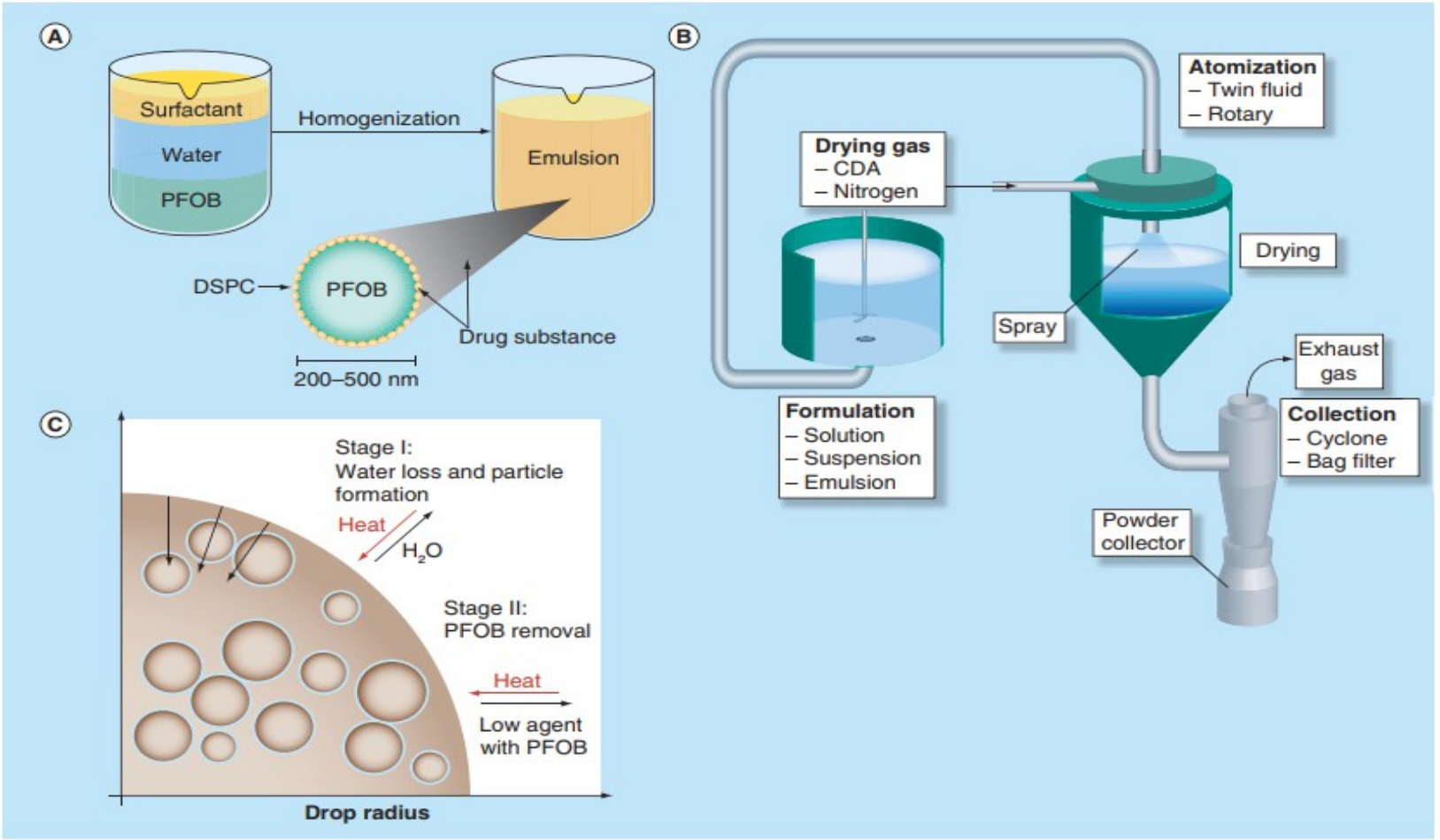

Figure 2. PulmoSphere™ particles are manufactured using an emulsion based spray–drying process. (A) Submicron

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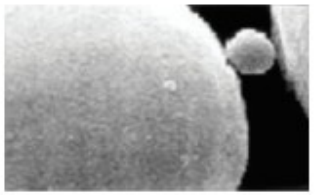
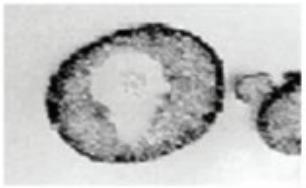
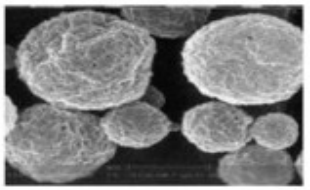
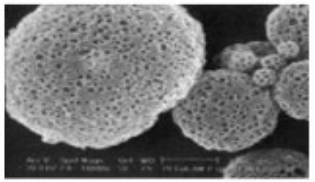
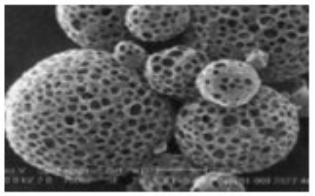
Table 2. Influence of the volume fraction of oil phase of particle properties for a 50% w/w formulation of gentamicin sulfate.

ϕ_{PFOB}	TEM	SEM	VMD (μm)	Surface area (m^2/g)	ρ_{tapped} (g/cm^3)	Porosity (%)
0			3.0	2.0	1.24	1.9
0.1			3.4	25.7	0.35	72.3
0.3			5.8	72.4	0.17	86.6
0.5			7.3	56.9	0.05	96.0

Particle cross-sections were imaged with TEM, while particle morphologies were imaged with SEM. The VMD was obtained via laser diffraction.
ϕ_{PFOB}: Volume fraction of perfluorooctyl bromide; ρ_{tapped}: Tapped density; SEM: Scanning electron microscopy; TEM: Transmission electron microscopy; VMD: Volume weight mean diameter.
Adapted with permission from [3] © Virginia Commonwealth University (2000).

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Table 3. Clinical development with PulmoSphere™ formulations (as of June, 2013).

API	PSph format	Delivery system	Status	Studies	Ref.
Tobramycin	Solution PulmoSphere™	DPI (T-326)	Approved	Marketed drug product for treating chronic *Pseudomonas aeruginosa* infections in CF patients. Five completed clinical studies encompassing more than 500 subjects	[11,38–44]
Ciprofloxacin	Suspension PulmoSphere	DPI (T-326)	Phase III	Completed clinical development through Phase IIb in CF and non-CF bronchiectasis. Five completed studies encompassing more than 400 subjects	[46–50]
Glycopyrrolate/formoterol, glycopyrrolate, formoterol	Carrier PulmoSphere	pMDI	Phase III	Completed clinical development through Phase IIb: ten studies encompassing more than 1000 subjects (COPD)	[51,52]
Amphotericin B	Suspension PulmoSphere	DPI (T-326)	End of Phase II	Completed three Phase I studies in 57 healthy volunteers. Completed end of Phase II meetings with Health Authorities for prophylaxis against invasive pulmonary aspergillosis indication.	[Nektar Therapeutics, Unpublished Data]
Glycopyrrolate/ Formoterol/ Budesonide	Carrier PulmoSphere	pMDI	Phase I	A Phase I study was initiated with the triple combination for COPD	[76]
Indacaterol	Suspension PulmoSphere	DPI (Concept1, Simoon)	Proof of concept	Completed three studies with more than 100 subjects	[Novartis Pharmaceuticals Corporation, Unpublished Data]
Budesonide	Suspension PulmoSphere	DPI (Eclipse®)	Proof of concept	Pharmacoscintigraphy study exploring flow rate dependence of budesonide PulmoSphere relative to Pulmicort® Turbuhaler® in ten healthy volunteers	[10]
Leuprolide	Solution PulmoSphere	DPI (Turbospin®)	Proof of concept	Pharmacokinetics study in 12 healthy volunteers	[Inhale Therapeutic Systems, Unpublished Data]
Albuterol	Solution PulmoSphere	pMDI	Proof of concept	γ scintigraphy study comparing albuterol PulmoSphere formulation to Ventolin® Evohaler® in nine healthy volunteers	[22]

API: Active pharmaceutical ingredient; CF: Cystic fibrosis; COPD: Chronic obstructive pulmonary disease; DPI: Dry-powder inhaler; pMDI: Pressurized metered-dose inhaler; PSph: Phosphoserine phosphatase.

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"Large doses of PFOB (up to 30 ml/kg body weight) have been instilled into the lungs in support of partial liquid ventilation. Based on pulmonary safety studies in non-human primates, the calculated permitted daily exposure according to residual solvent guidelines set by the International Conference on Harmonization of Technical Requirements of Pharmaceuticals for Human Use (ICH Q3C) is about 1 g/day [Alliance Pharmaceutical Corporation,Unpublished Data].

This is orders of magnitude in excess of the anticipated **PFOB levels delivered in PulmoSphere powders, where residual concentrations of less than 0.5% w/w are typically measured in spray–dried powders**."

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Effects of perfluorocarbon emulsions on human fibroblasts and effects of emulsion storage temperature on particle size distribution

Valérie Centis, Charles J. Doillon, Patrick Vermette

3.2 Abstract

The purpose of this study was to characterize emulsion preparations made of perfluorooctyl bromide (PFOB) and egg yolk phospholipid (EYP) and their cytotoxicity. Dynamic light scattering and transmission electron microscopy revealed that freshly prepared emulsions stored at different temperatures for a 24-hour period have a unimodal particle size distribution with an average particle size of ca. 200 nm. The emulsion displayed a broader particle size distribution following 14-day storage. Primary human fibroblasts exposure to PFOB/EYP emulsions permanently inhibited cell proliferation and decreased mitochondrial activity. Scanning electron microscopy pictures reveal the presence of spherical particles on the fibroblasts following exposure to the emulsions after thorough rinsing with culture media.

Keywords: Perfluorocarbon emulsions, PFOB, oxygen carriers, cytotoxicity, fibroblasts, cell morphology, cytocompatibility.

Valerie Centis Thesis 2009

Alternative Technologies

Co-solvent systems

Alternative propellant

Softmist spray