흡입약제 - 어떻게 선택하고 유지할 것인가?

울산대학교병원 | 호흡기내과 | **나승원**

2021년 10월 30일 일선진료의를 위한 호흡기질환 심포지엄

ULSAN
UNIVERSITY
HOSPITAL

올바른 흡입기 사용법

SCAN ME

그동안 잘못 사용했네요
뭔가 늘 그닥 효과를 못보는 것같더니..
잘배우고 갑니다
감사합니다

김혜윤 7개월 전
여태 잘못 사용했네요ㅠㅠ
자세한 정보 진심 감사드립니다~^^

Casey Hong 2년 전
천식으로 고생인데 흡입제써도 차도가없다했더니 여태 잘못썼네요ㅜㅜ감사합니다
1 답글

_꽁네 3년 전
헐 나는 천식 2년 째인데 어쩐지 숨이 안쉬어지더라...

Hey_you LaLaLa 1년 전
감사합니다 수평으로 들이마셔야 하는지 몰랐는데 이제 바르게 할 수 있겠어요!

올바른 스페이서 사용법

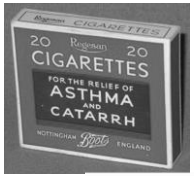
스페이서 구입 연락처

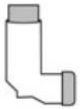
흡입약제 선택과 유지

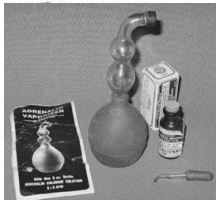
강의 순서

- 흡입약제의 역사와 적용 질환
- 흡입제 관련 용어 이해하기
- 흡입기/흡입약제의 종류, 특징, 선택
- 흡입기 저항에 따른 사용법 차이
- 잘못된 흡입기 사용과 보완을 위한 보조기기

Milestones in the development of inhaler therapy







First pressurized inhaler

Medihaler CFC-pMDI
Isoprenaline and adrenaline
(Riker Laboratories)

Spinhaler® DPI
Sodium cromoglycate
(Fisons)

Rotahaler® DPI
Salbutamol
(Allen & Hanburys)

Airomir™ HFA-pMDI
Albuterol sulfate
(3M Health Care)

1850 1858 1864 1930 1948 1956 1967 1969 1987 1994 2012 2015

First DPI

Glass- or plastic-bulb nebulizers
Adrenaline chloride

Aerohaler® DPI
Penicillin
(Abbot)

Diskhaler® DPI
Salbutamol
(Allen & Hanburys)

Turbuhaler® DPI
Budesonide
(AstraZeneca)

Respimat®
(Soft Mist)
Tiotropium
(Boehringer Ingelheim)

Stein W et al. J Aerosol Med Pulm Drug Deliv. 2017;30(1):20-41
Roche N et al. J Aerosol Med Pulm Drug Deliv. 2016;29(4):311-327

Inhalation as a route for drug delivery

- Targeted local delivery
- Less systemic side effects
- Smaller therapeutic doses required
- Rapid onset

Indication

- **Airway diseases**
- **Bronchiectasis**
- **Pulmonary HTN**
- **MDR TB**
- **Vaccination**
- **Parkinson’s disease**

Definitions of commonly used terms that describe an aerosol

- **Labelled** dose or **nominal** dose:
  - The dose that is metered.

- Total **emitted** dose or **delivered** dose:
  - The mass of drug emitted per actuation that is actually available for inhalation at the mouth.

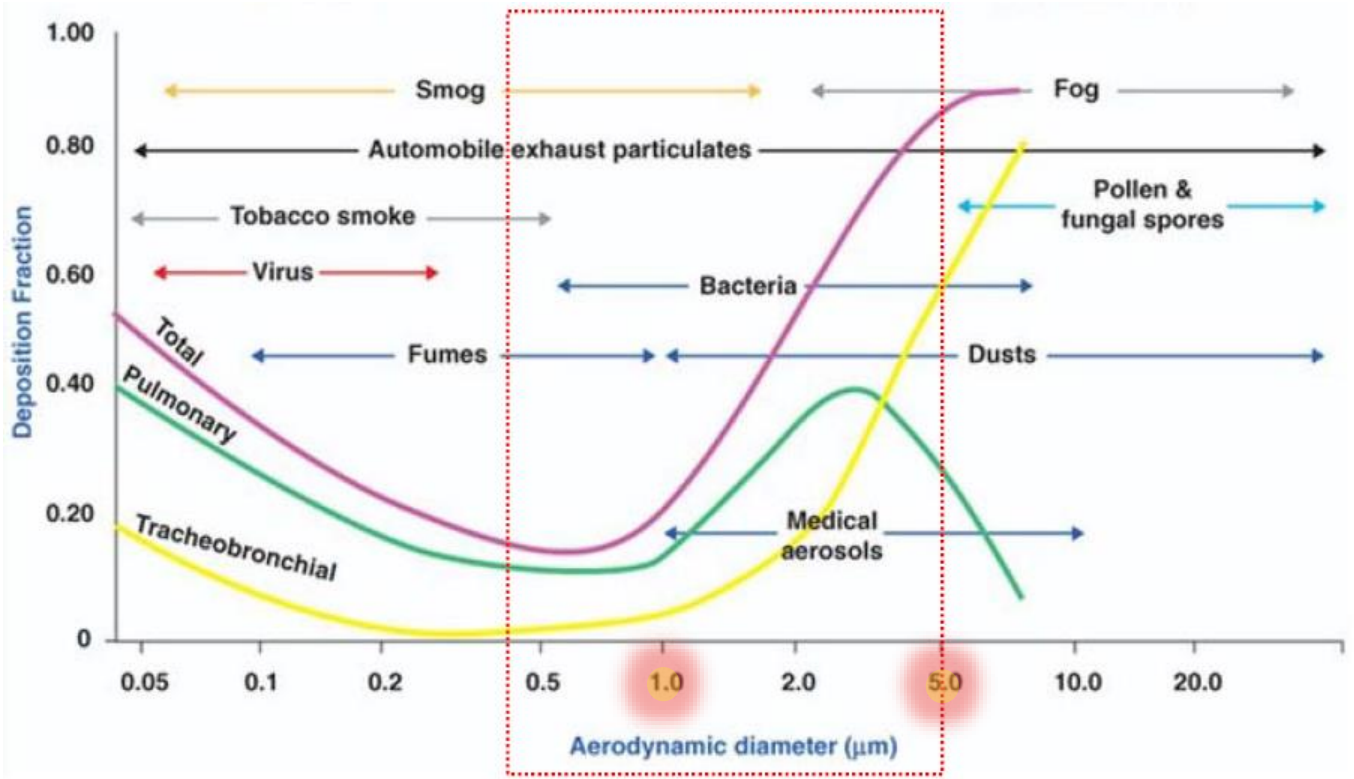
Eur Respir J 2011; 37: 1308–1331

TABLE 1 Definitions of commonly used terms that describe an aerosol

Fine-particle dose	FPD	The mass of particles <5 μm in size within the total emitted dose.
Fine-particle fraction	FPF	The fine particle dose divided by the total emitted dose.
Aerodynamic equivalent diameter	d_{ae}	The diameter of a fictitious sphere of unit density (1 $g \cdot cm^{-3}$) that has the same gravitational (settling) velocity in the same gas as the actual particle.
Mass median aerodynamic diameter	$d_{ae,\mu m}$ or MMAD	The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.

Eur Respir J 2011; 37: 1308–1331

Deposition of Aerosols by Aerodynamic diameter



CP Yu, et al. Am Ind Hyg Assoc J 1979:40;999-1005

Aerodynamic diameter

Non spherical particle

d_{ev} = 0.45 µm
ρ_p = 6000 kg.m^{-3}
χ = 1.4

V_s = 0.035 mm.s^{-1}

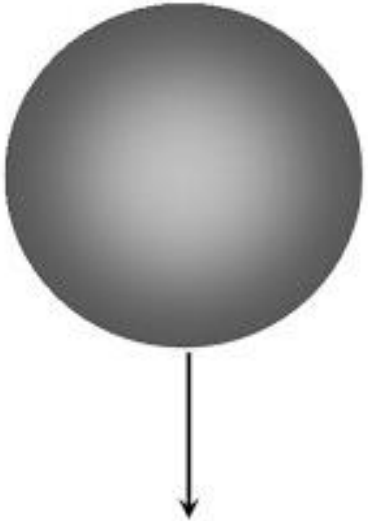
Stokes diameter

d_S = 0.37 µm
ρ_p = 6000 kg.m^{-3}
χ = 1

V_s = 0.035 mm.s^{-1}

Aerodynamic diameter

d_a = 1.0 µm
ρ_0= 1000 kg.m^{-3}
χ = 1

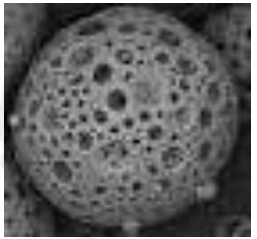


V_s = 0.035 mm.s^{-1}

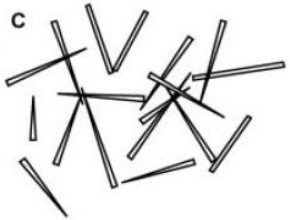
A

$$D_{ae} = D_{eq}\sqrt{\left(\frac{\rho_p}{\rho_o X}\right)}$$

B

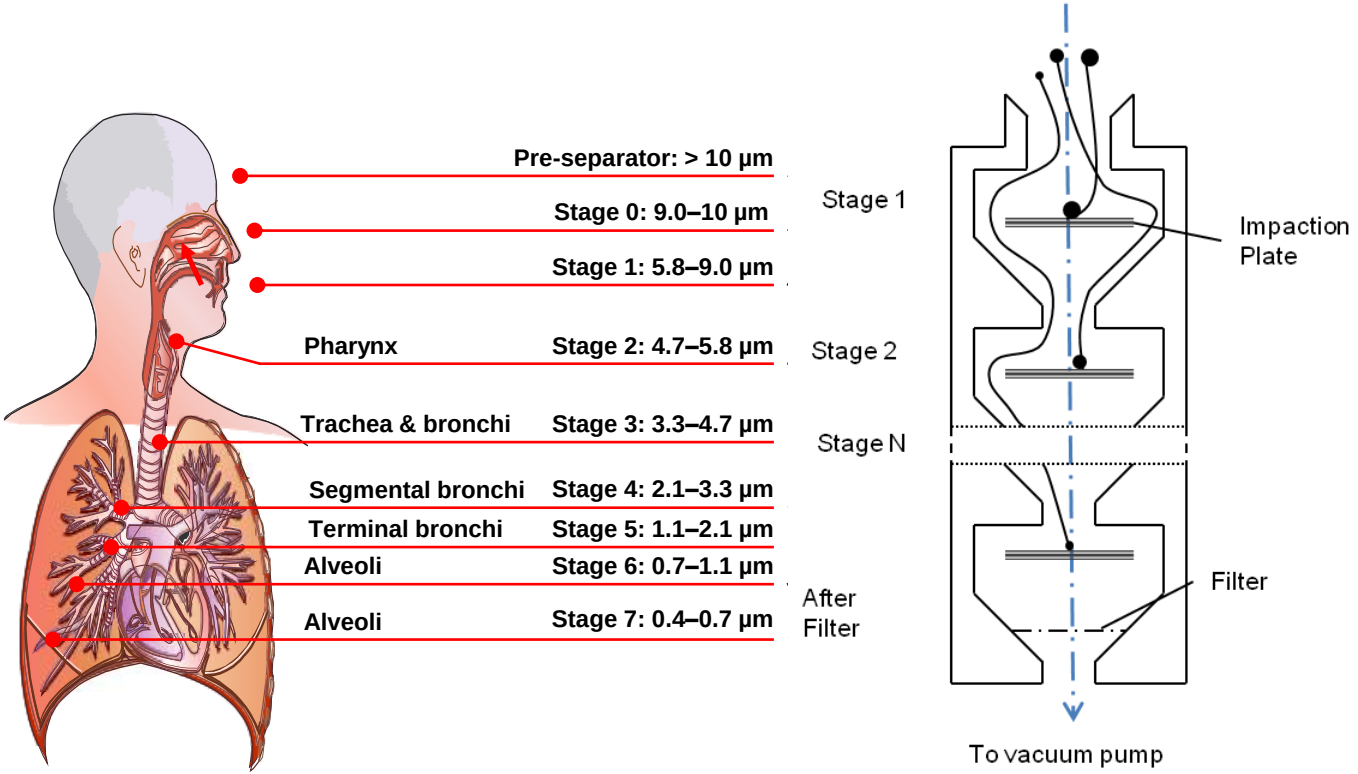


C



Nanoengineering. Global Approaches to Health and Safety Issues, 2015, Pages 55-84
Respir Care. 2005 Sep;50(9):1209-27.

Determining the in vitro fine-particle fraction of an aerosol: Andersen Cascade Impactor

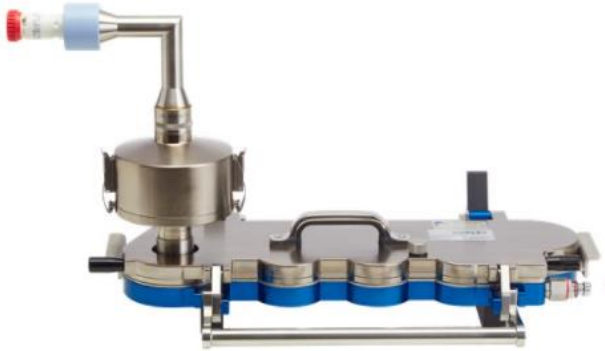


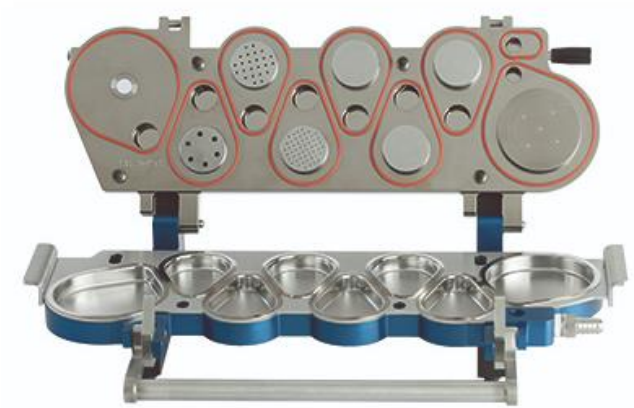
Particle size analysis of aerosols from medicinal inhalers. KONA 2004;22:32–65

Andersen Cascade Impactor (ACI)

Int J Pharm. 2016;514(2):420-427.

NGI: Next Generation Pharmaceutical Impactor

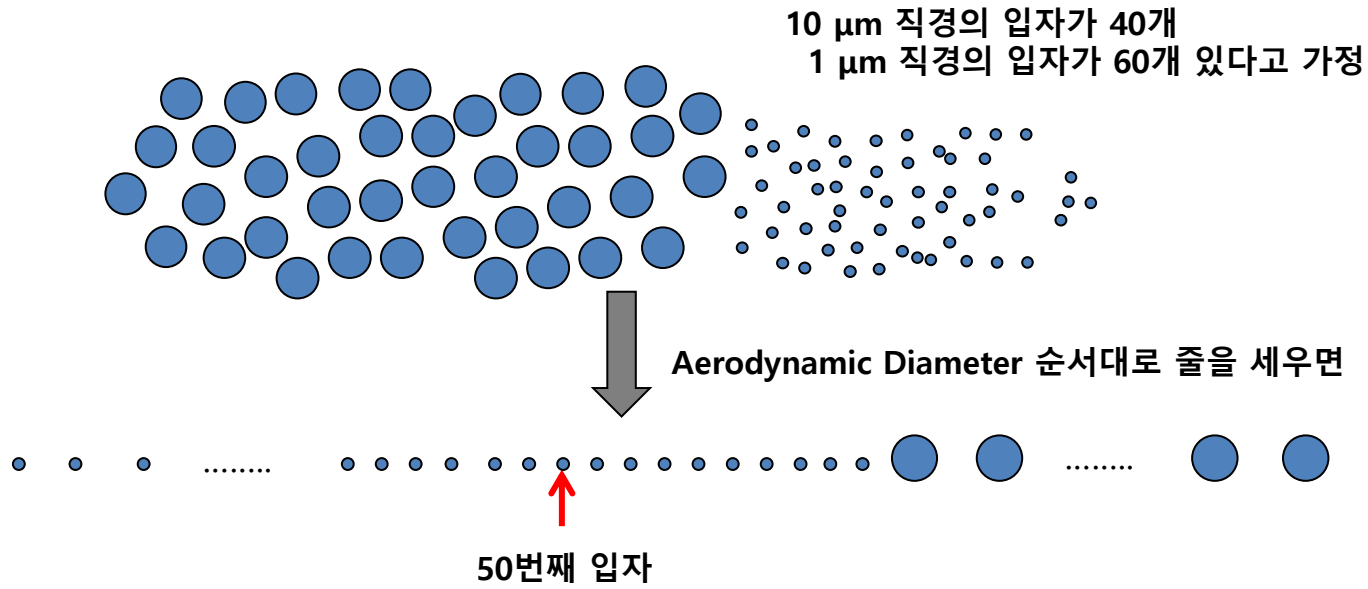




https://www.copleyscientific.com/inhaler-testing/

MMAD (Mass Median Aerodynamic Diameter)

- MMAD 정의: 상위 50% 또는 하위 50% 에 있는 입자의 Aerodynamic Diameter



Cristopher et al. Alternative Approaches to MMAD determination.

Inhaler types

- **Metered Dose Inhalers (MDI)** – Evohaler, Rapihaler
  - Pressurized MDI = pMDI
  - Breath Actuated pMDI = BA-pMDI or BAI
- **Soft Mist Inhalers (SMI)** – Respimat
- **Dry Powder Inhaler (DPI)** – Turbuhaler, Diskus, Handihaler, Breezhaler, Ellipta, Genuair, Nexthaler, Spiromax, ….

pMDI

pMDI + spacer

Evohaler

Rapihaler

Soft Mist Inhaler

Respimat

Choosing Inhalers in Korea

- DPI
  - Handihaler
  - Swinghaler
  - Turbuhaler
  - Diskus





Breezhaler

Ellipta


Genuair


Nexthaler

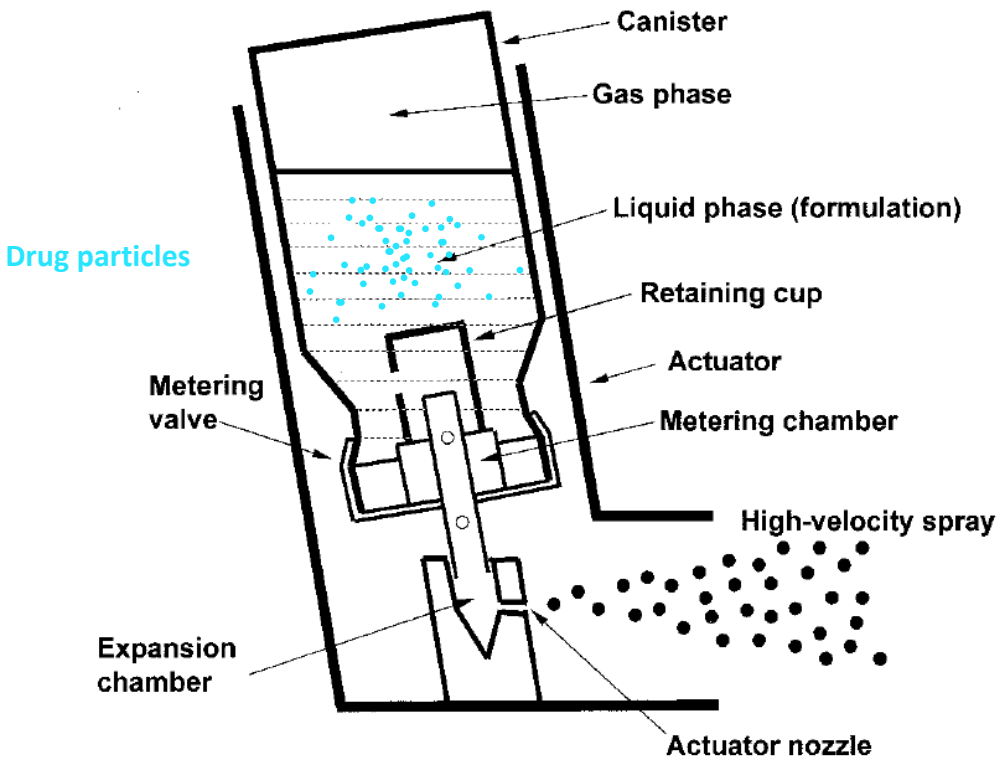
Spiromax

Has Patient Technique Improved Over Time?

Currently, there are over **230** **device & drug combinations** available

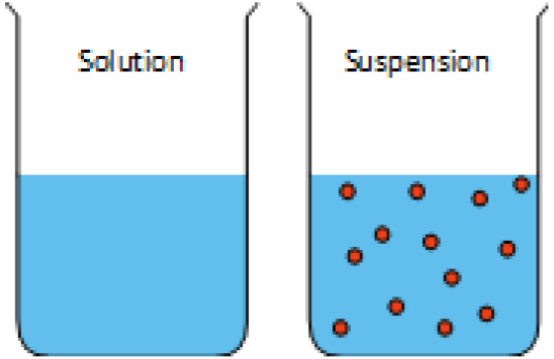
CHEST 2016;150(2):394-406

pMDI (Pressurized Metered Dose Inhalers)

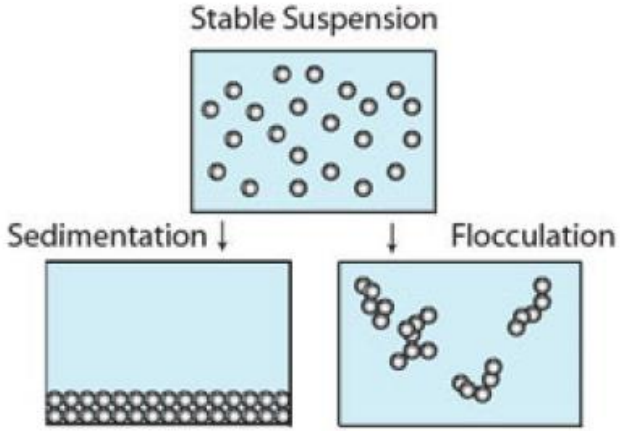


Stephen P Newman. Respir Care 2005;50(9):1177–1188

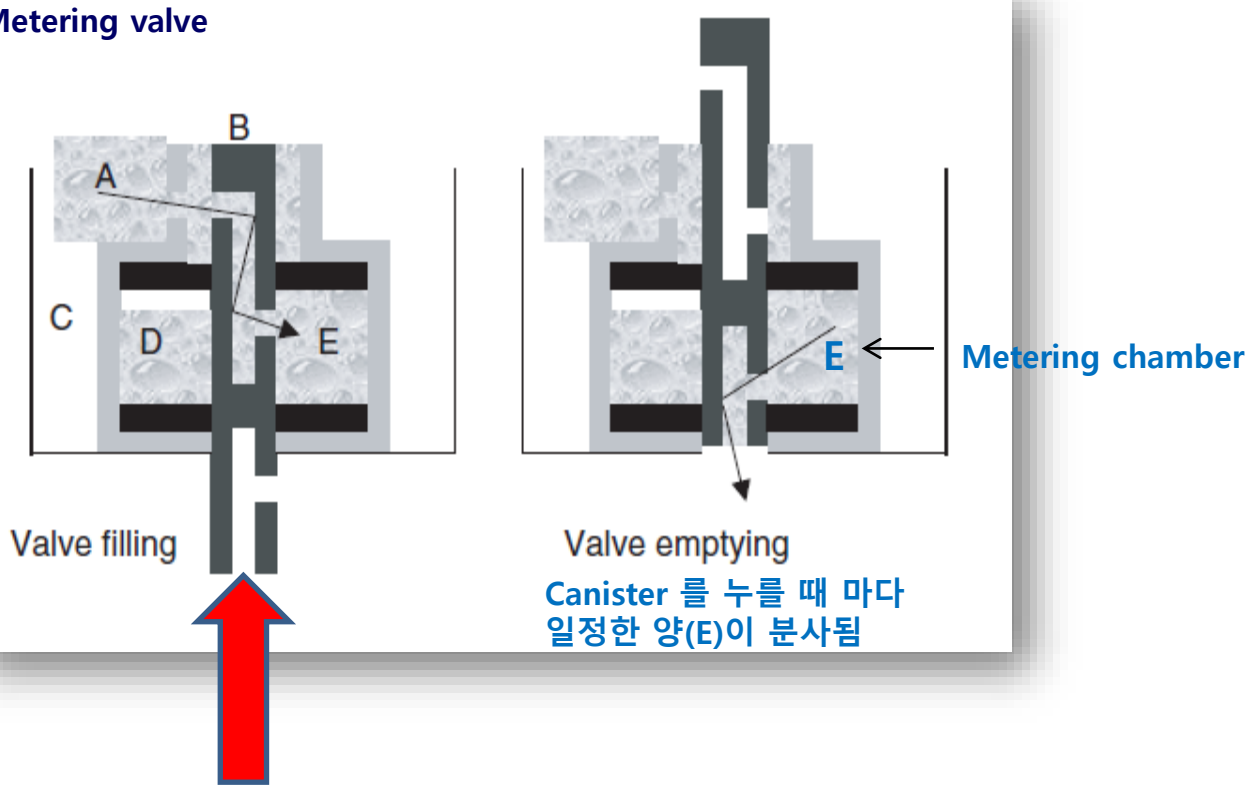
pMDI - Solution vs. Suspension



높다	물리적 안정성	낮다
낮다	화학적 안정성	높다



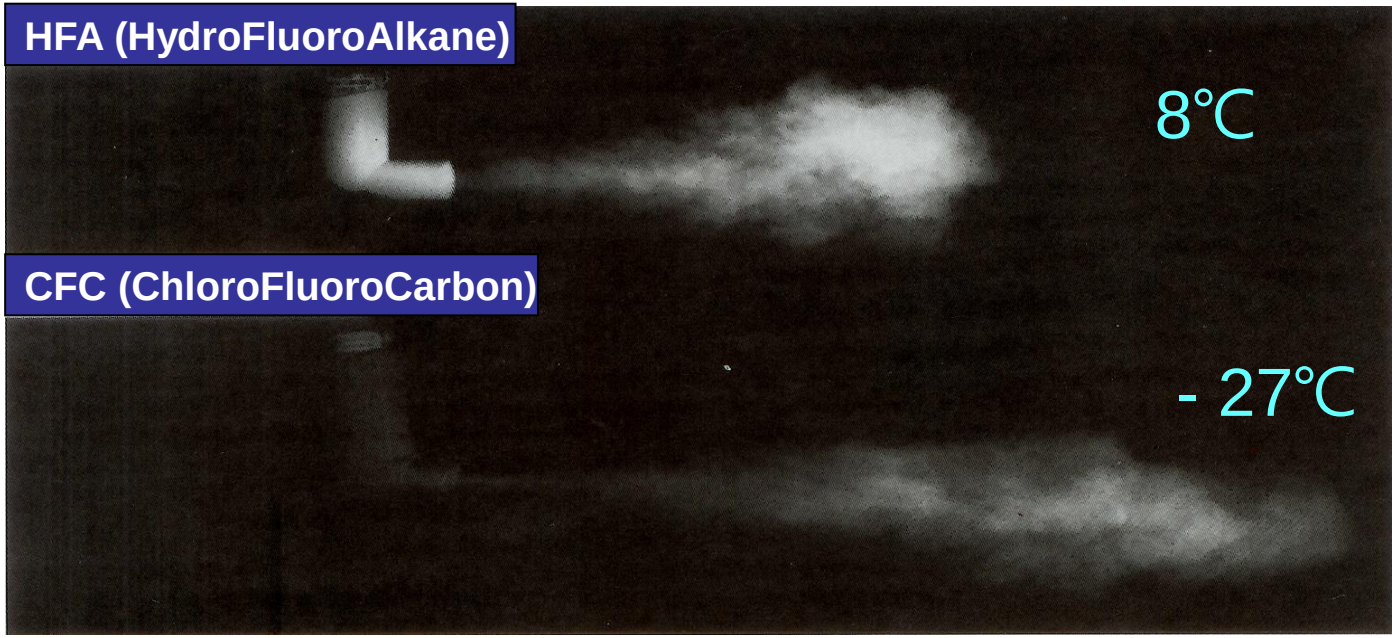
Metering valve



Canister 를 누를 때 마다
일정한 양(E)이 분사됨

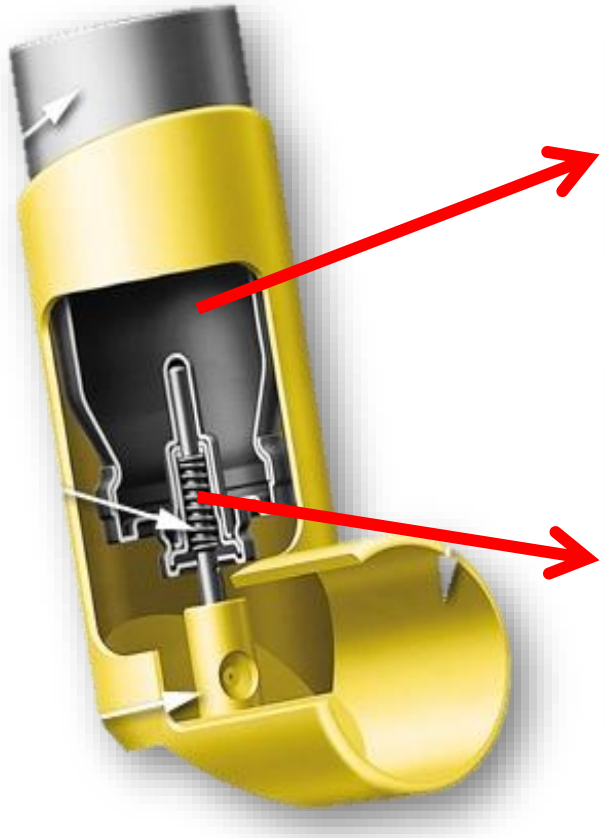
Hugh DC Smyth. Exper Opin Drug Deliv. 2005;2(1):53-74

pMDI 추진제: HFA vs CFC



- HFA 장점: ethanol이 함유되어 속도가 더 느리며, 더 따뜻해서 cold freon effect가 더 적음.
- 보다 작은 particle로 일정한 drug delivery.

pMDI formulation



약물, 추진제 (HFA) & 용매

- Solution or Suspension
- Ethanol 첨가 (약제 용해 용이)

약제 뭉침 방지, 밸브윤활

- 계면활성제 (0.1~2%)

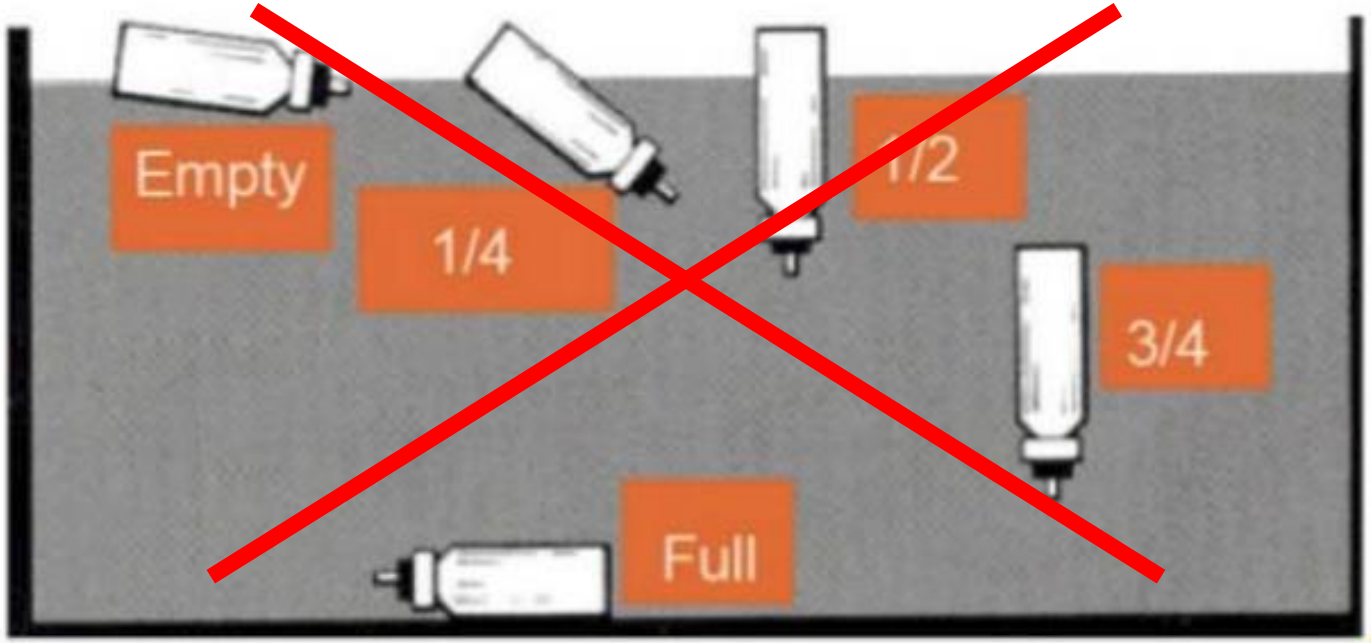
  Oleic acid, Sorbitan trioleate, Lecithin
- 산화방지제 (ascorbic acid)
- 첨가제, 향료 etc.

Guidance for Industry

Integration of Dose-Counting Mechanisms into MDI Drug Products

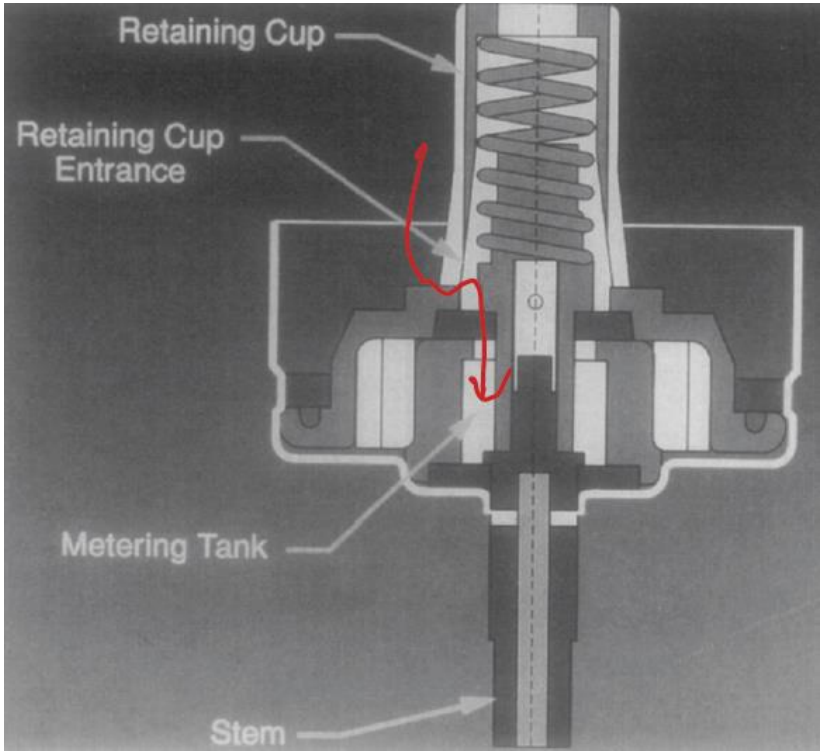
U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Clinical Medical
March 2003

Dose counter 없을 때 잔량 확인 – CFC 제제



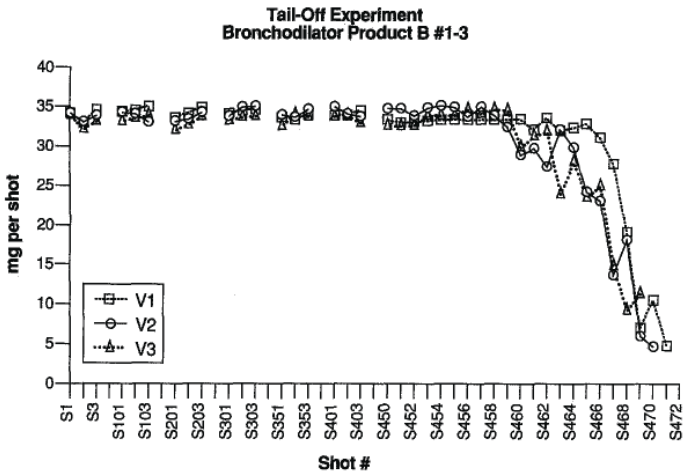
- HFA를 추진제로 사용하는 pMDI 제제는 습기에 **약하므로** 물에 넣으면 안됨 (잔량 확인 불가능)

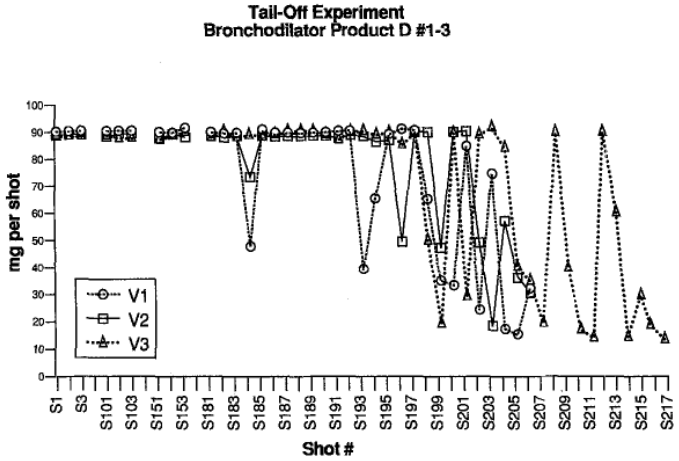
Tail off effect



Schultz RK. Drug delivery characteristics of metered-dose inhalers. J Allergy Clin Immunol. 1995;96(2):284-287.

Tail off effect





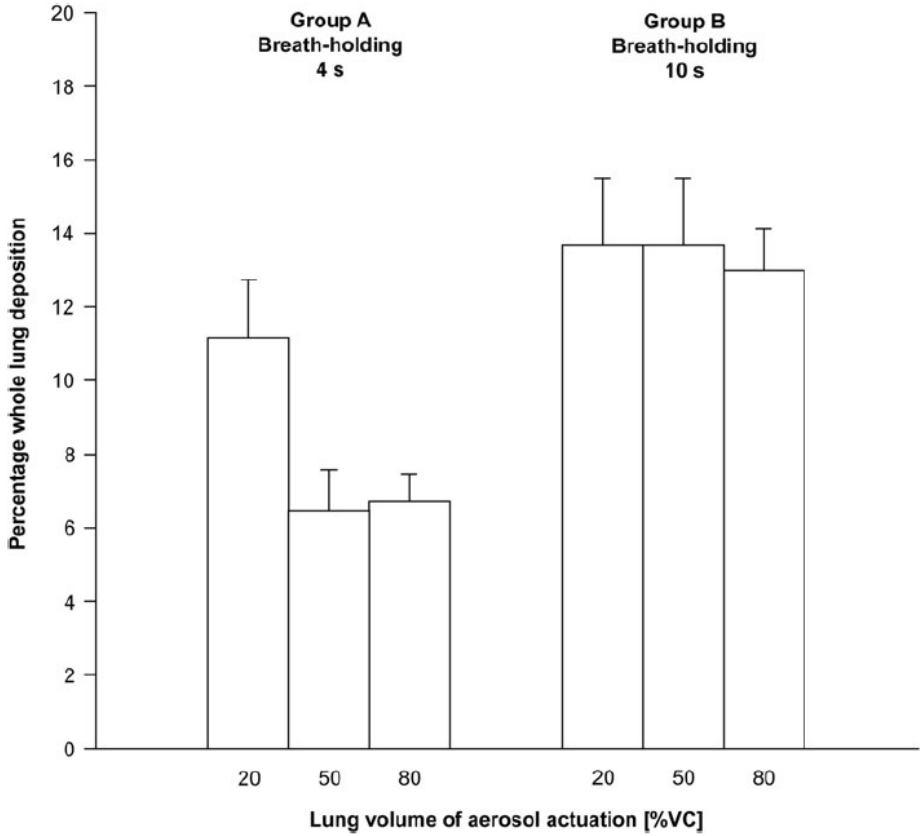
Schultz RK. Drug delivery characteristics of metered-dose inhalers. J Allergy Clin Immunol. 1995;96(2):284-287.

Problems patients have when using MDI

Inhale too fast	60%
Co-ordination failure	54%
Co-ordination failure and inhale too fast	92%
Stopping after inhalation (cold-freon effect)	24%

Spacers least preferred by patients

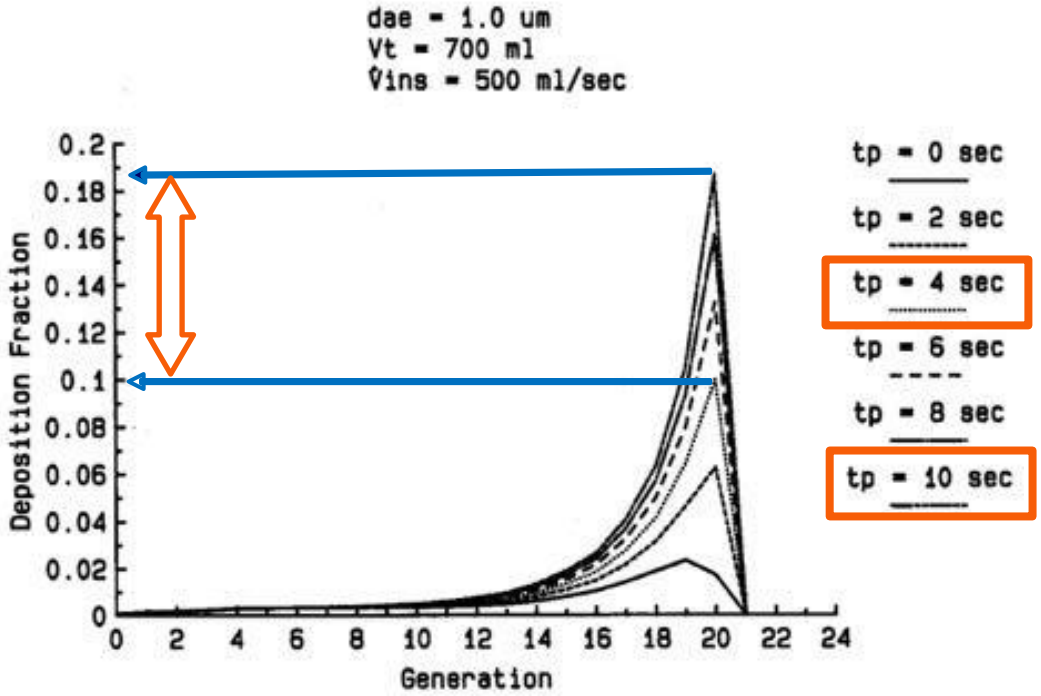
pMDI는 co-ordination이 완벽해야 하나?



Eur J Respir Dis Suppl. 1982;119:57-65.

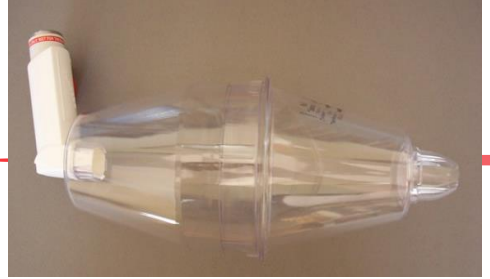
Importance of breath-holding for drug particles sedimentation

Deposition study with radiolabeled drug particles



Byron et al, Respiratory Drug Delivery, 1990

플루푸쉬



pMDI + Spacer

Large (600-800ml) vs Small (130-300ml) volume

Anti-Static Valved Holding Chamber

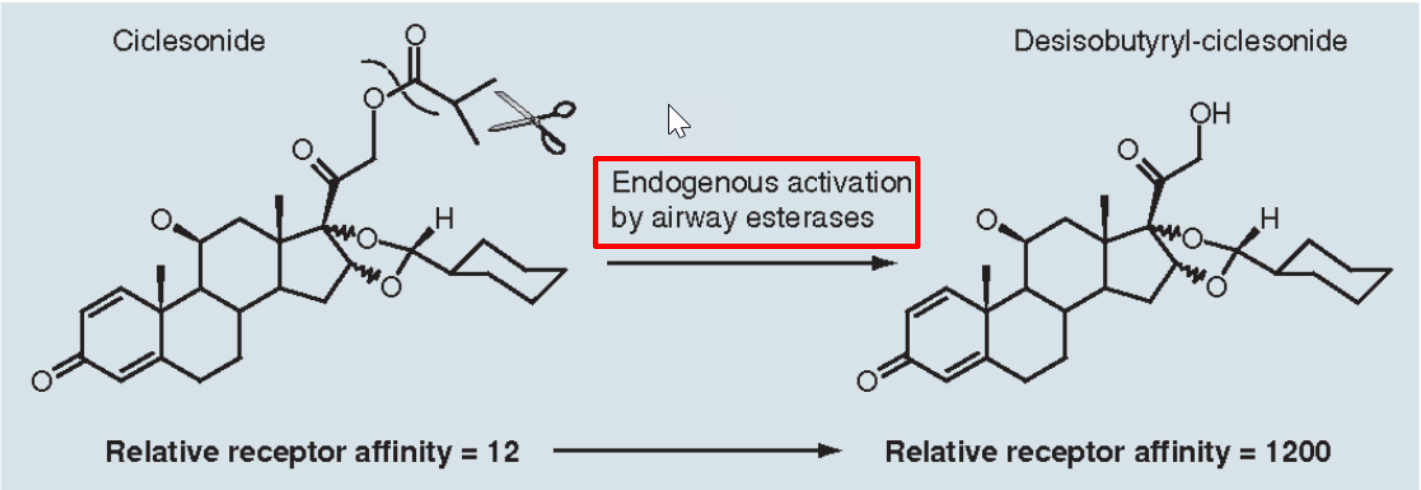
장점

- No need for hand-lung coordination
- Reduction of oral candidiasis
- Some spacers incorporate a whistle
  - Sound if inspiratory flow is too fast.

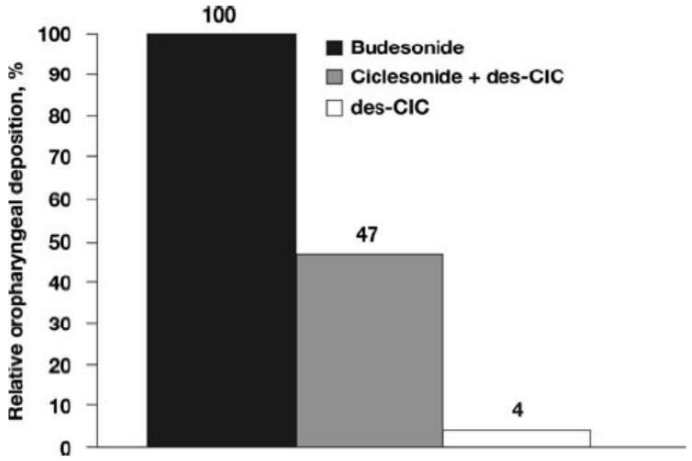
단점

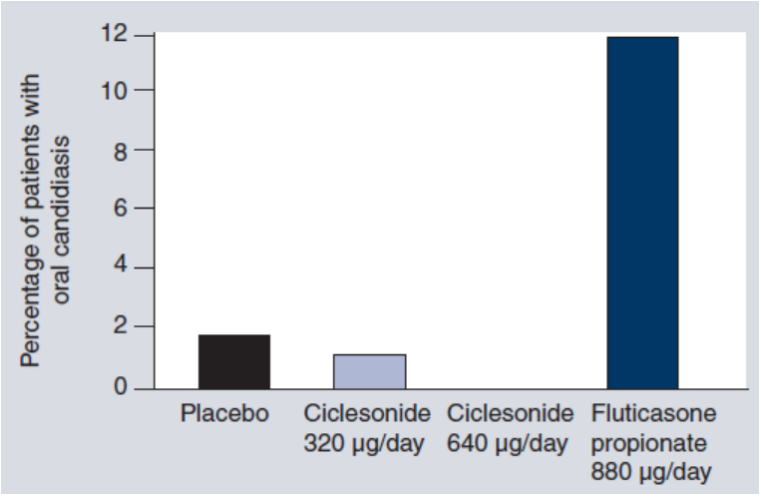
- Less portable than pMDI alone.
- Reduce drug delivery
  - Time delay for inhalation
  - Electrostatic charge

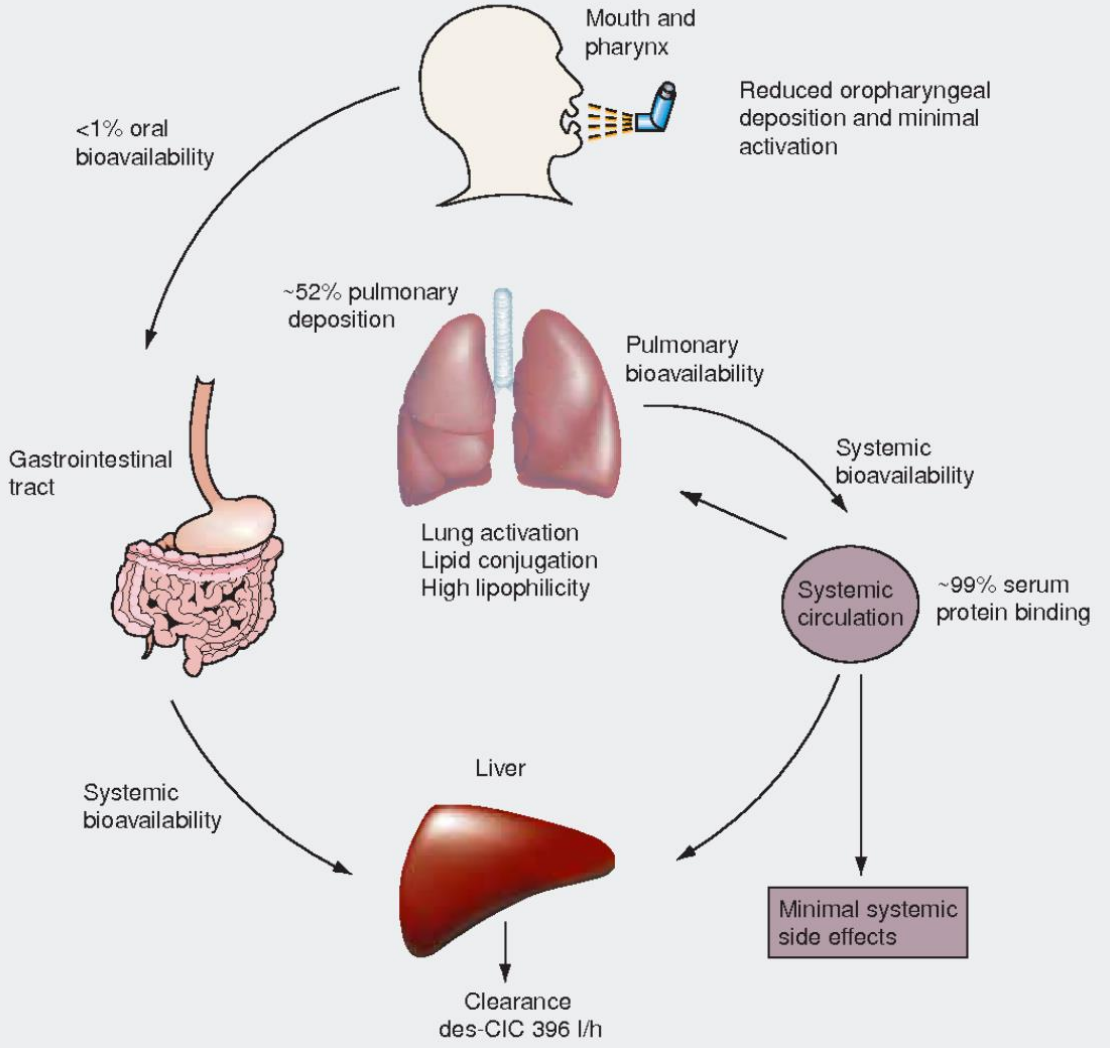
Ciclesonide metabolism



Journal of Pharmaceutical Sciences 105 (2016) 2509-2514
Berger, William E. Therapy (2005) 2(2), 167–178

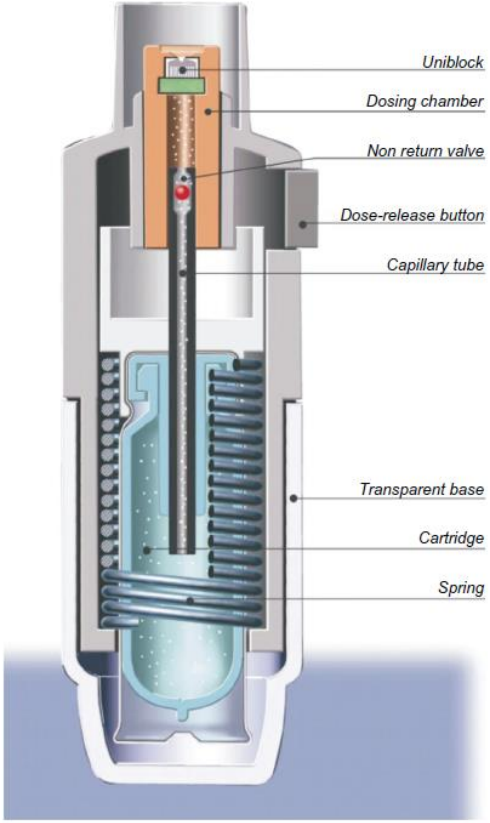




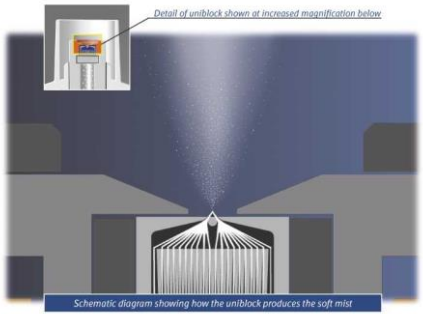


Eur J Clin Pharmacol (2005) 61: 203–208
Berger, William E. Therapy (2005) 2(2), 167–178

Respimat SMI (soft mist inhaler)



Uniblock structure



The cartridge

Dalby RN, et al. Medical Devices: Evidence and Research 2011;4:145–55.

Dry powder inhaler (DPI)

- Inspiratory volume & flow가 drug delivery를 결정하는 main factor
  - 환자의 흡입력에 의해 투여

- 장점
  - coordination이 필요 없다.
  - 추진제가 없어 cold freon effect 없고 친환경적

- 단점
  - 급성 악화시, 심한 기류 제한: 효과 떨어진다.
  - 습기에 약하다.
  - 잘 느껴지지 않는다.
  - 불어서 날아갈 수 있다.

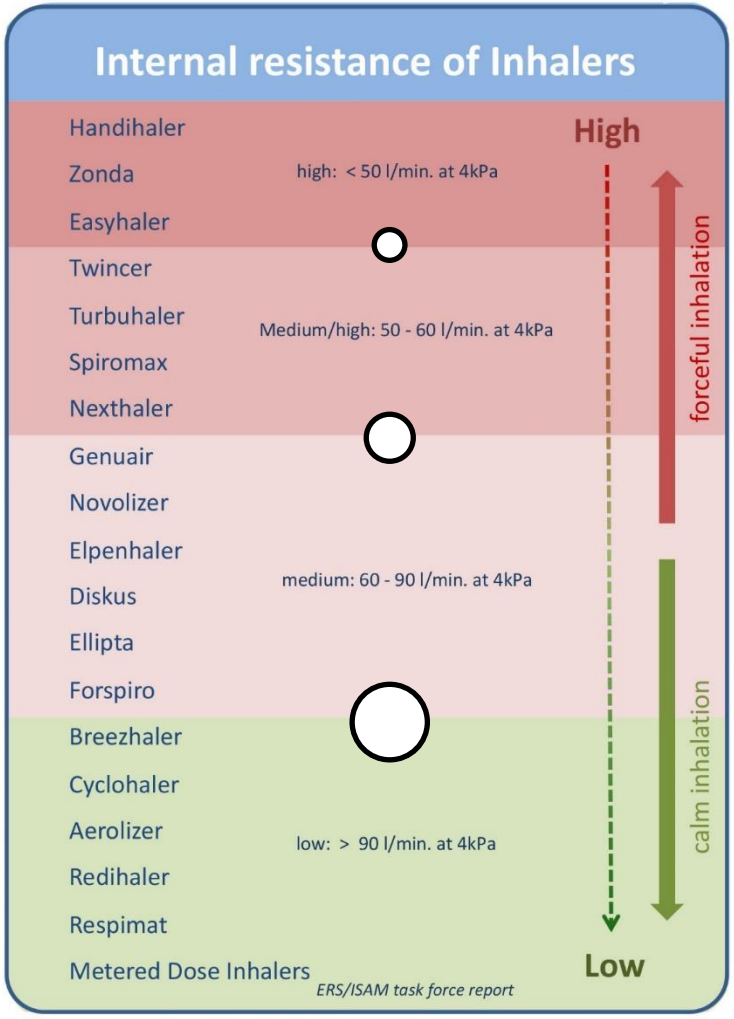
DPI 종류

Multi-dose DPIs

- Reservoir type
  - Nexthaler, Turbuhaler, Spiromax, Genuair
  - Others: Diskhaler (Rotadisk), Twisthaler, …..
- Blister type
  - Ellipta, Diskus

Single-dose capsule DPI

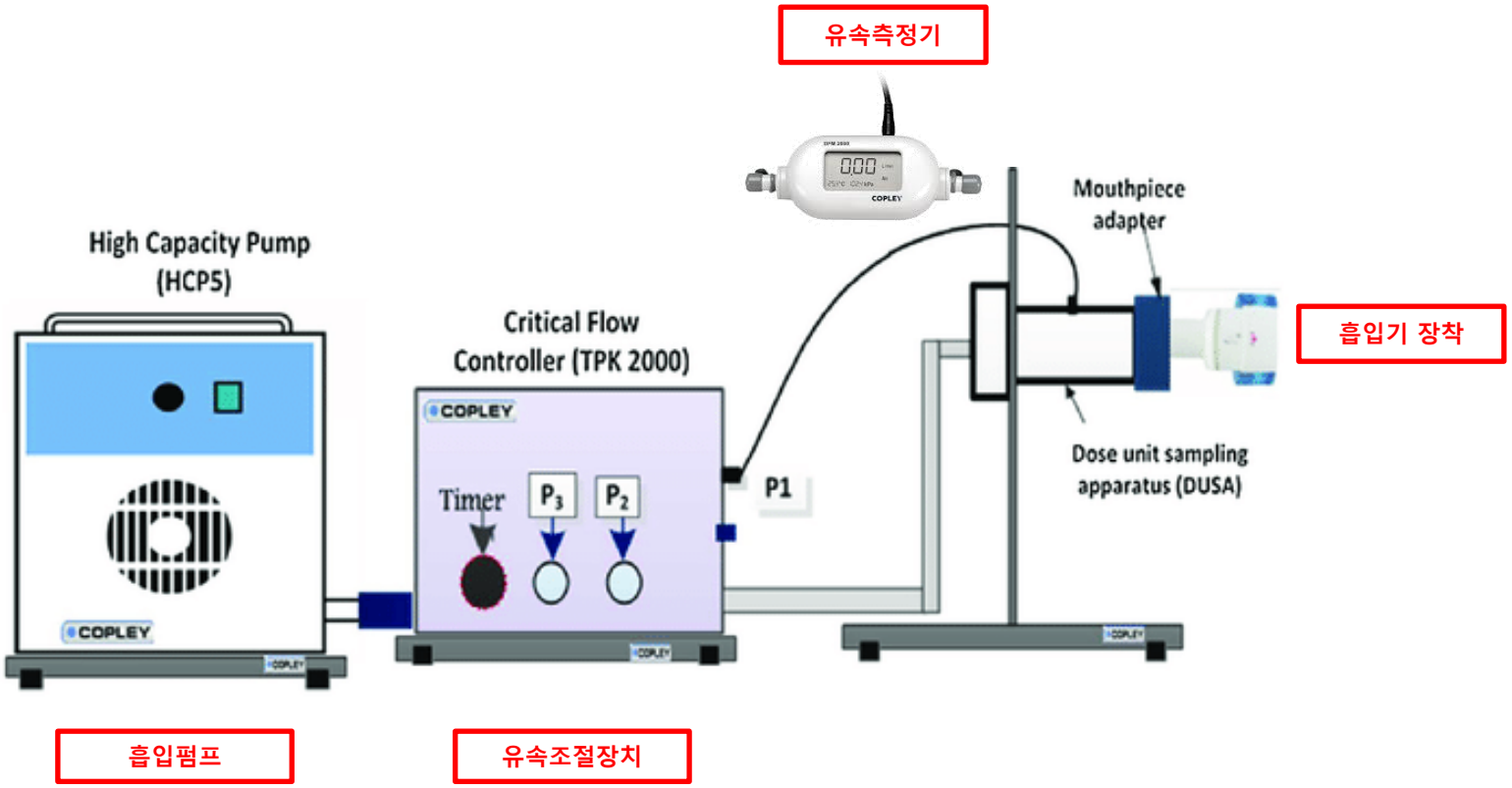
- Handihaler, Breezhaler



P. Hagedoorn, Pharmaceutical Technology and Biopharmacy, University of Groningen, Netherlands

$$\sqrt{\Delta P_D} = \sqrt{P_a - P_{oral}} = R_D\, Q$$

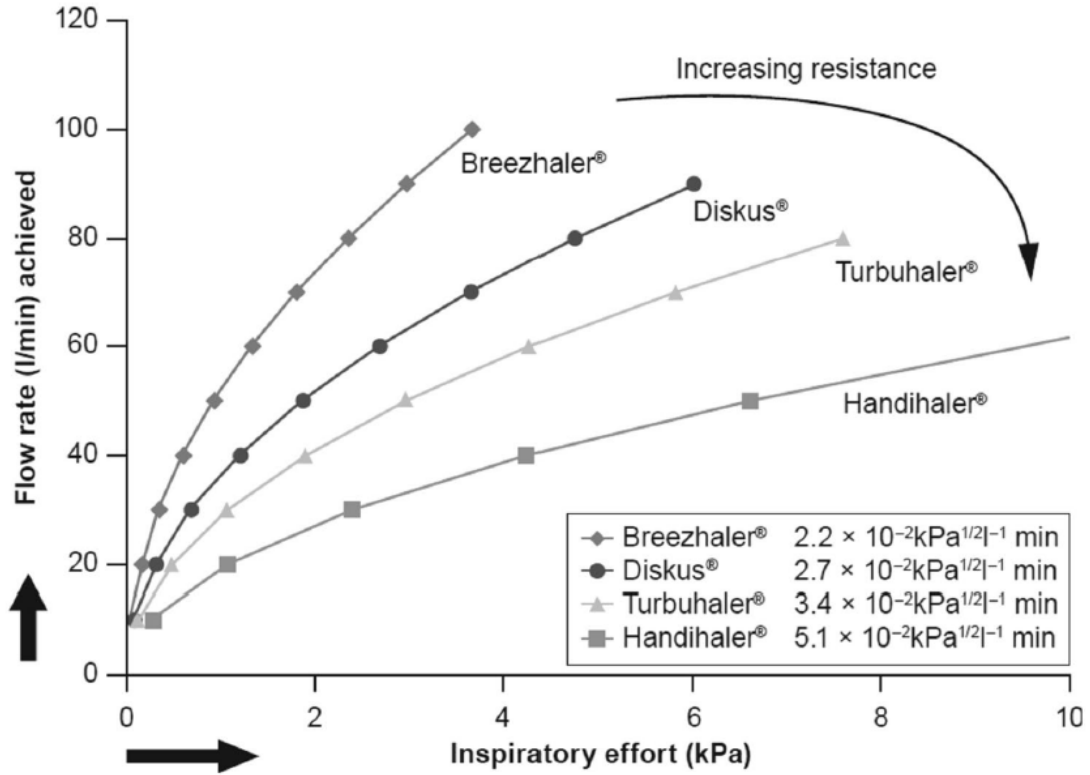
$$R_D = \sqrt{PD}/Q$$



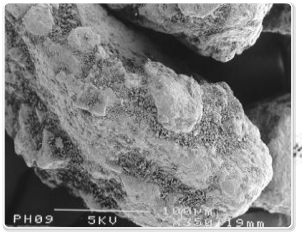
△ P : Pressure drop (4Kpa)
Q : Flow rate (L/min)
R : Device resistance

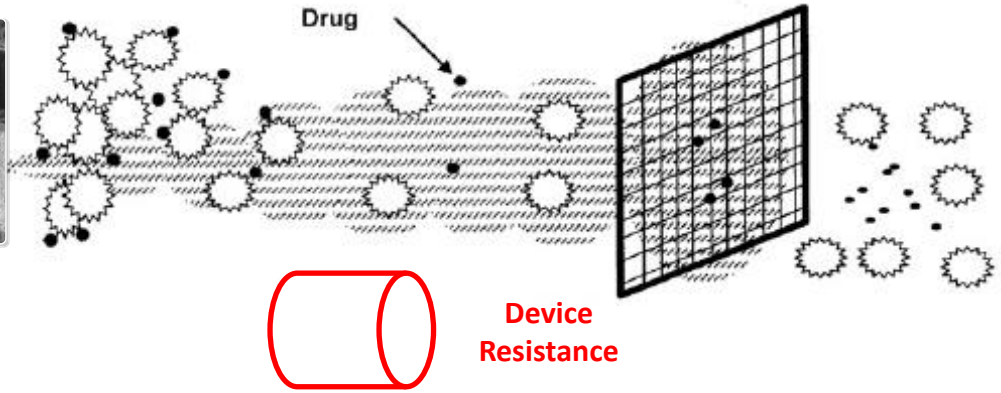
$$\text{Resistance} = \sqrt{\Delta P / Q}$$

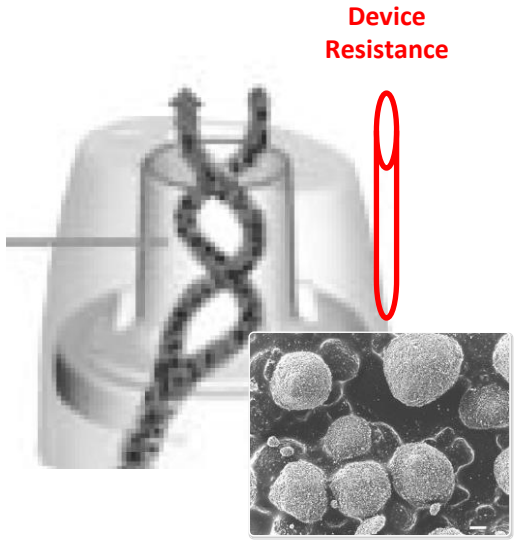
Flow rate at various inspiratory efforts through different DPI

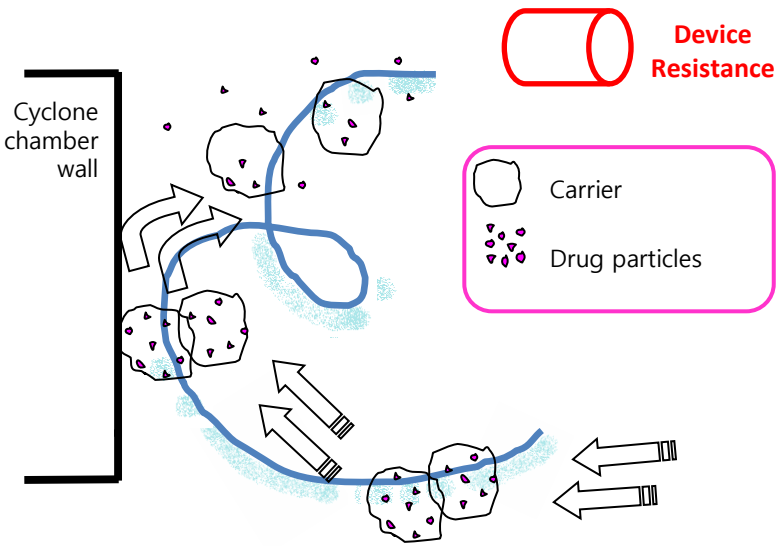


Clinical Drug Investigation (2021) 41:415–424

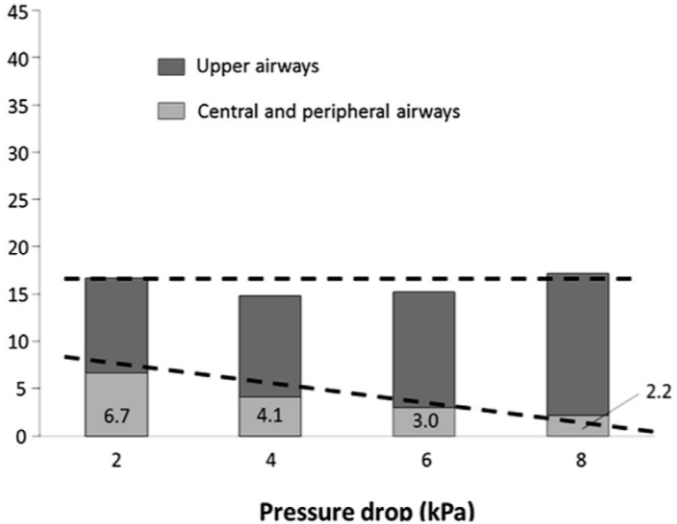

PH09 5KV

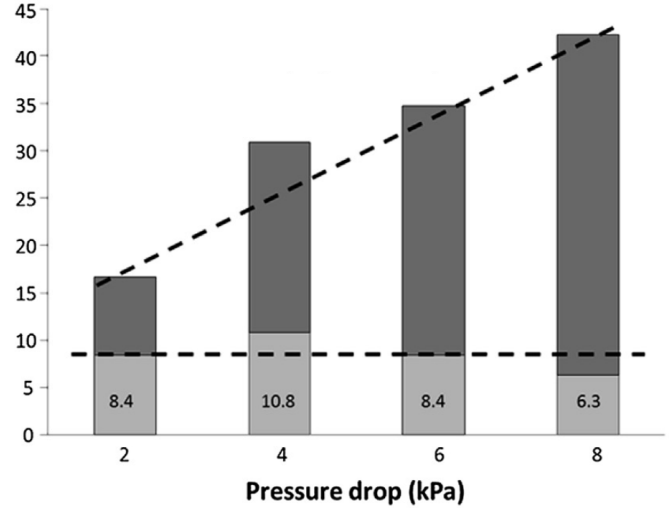

Drug
Device
Resistance

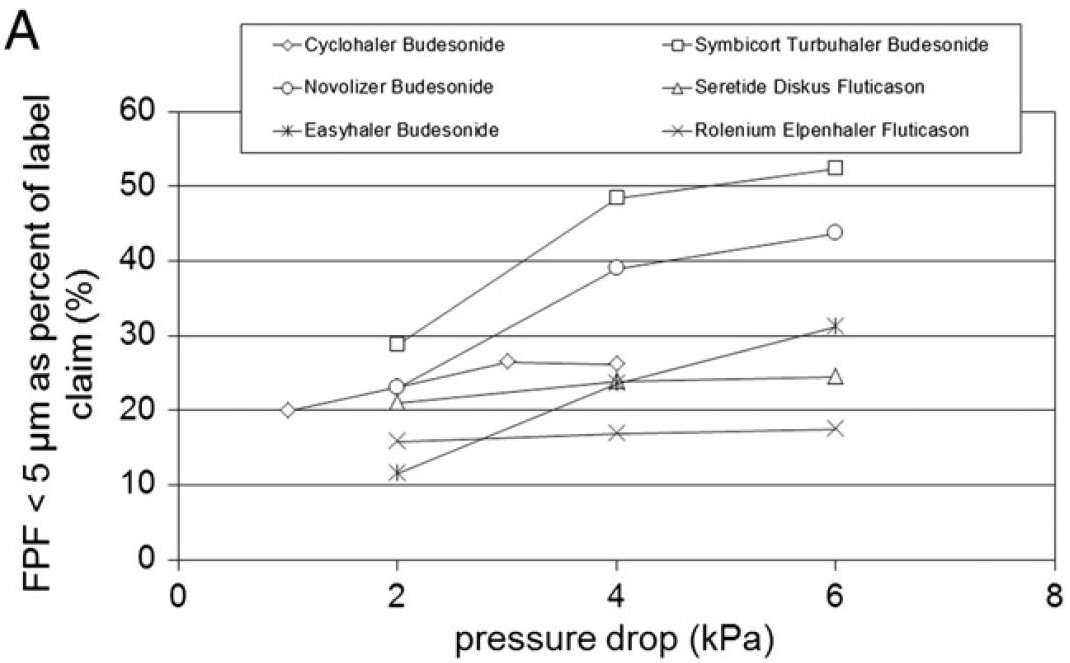

Device
Resistance


Device
Resistance
Cyclone
chamber
wall
Carrier
Drug particles

Flow-rate independent vs. dependent DPI

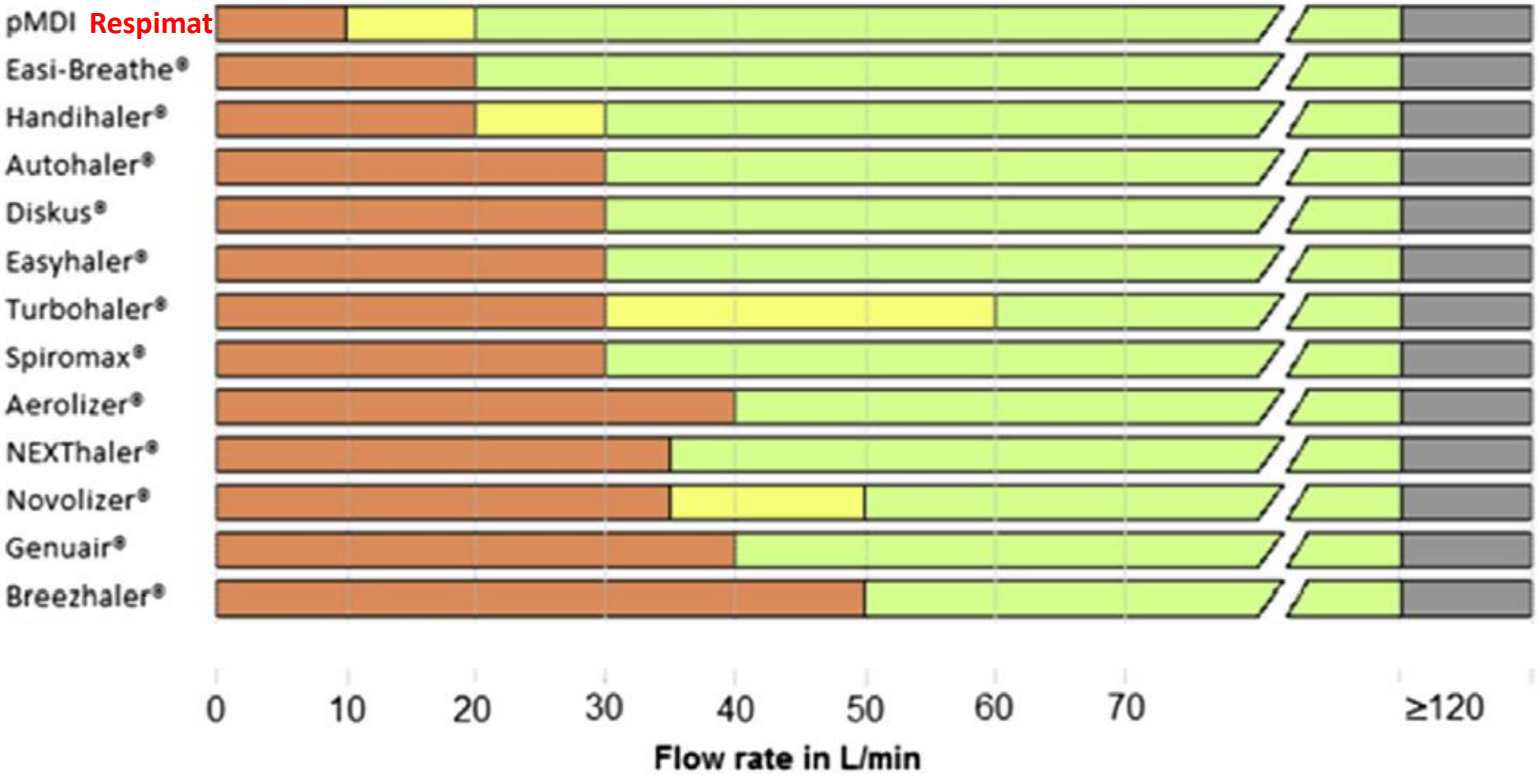






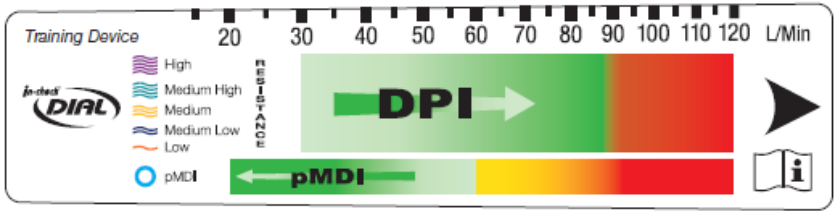
Respir Med. 2014;108(8):1195-203
Adv Drug Deliv Rev. 2014;75:18-31

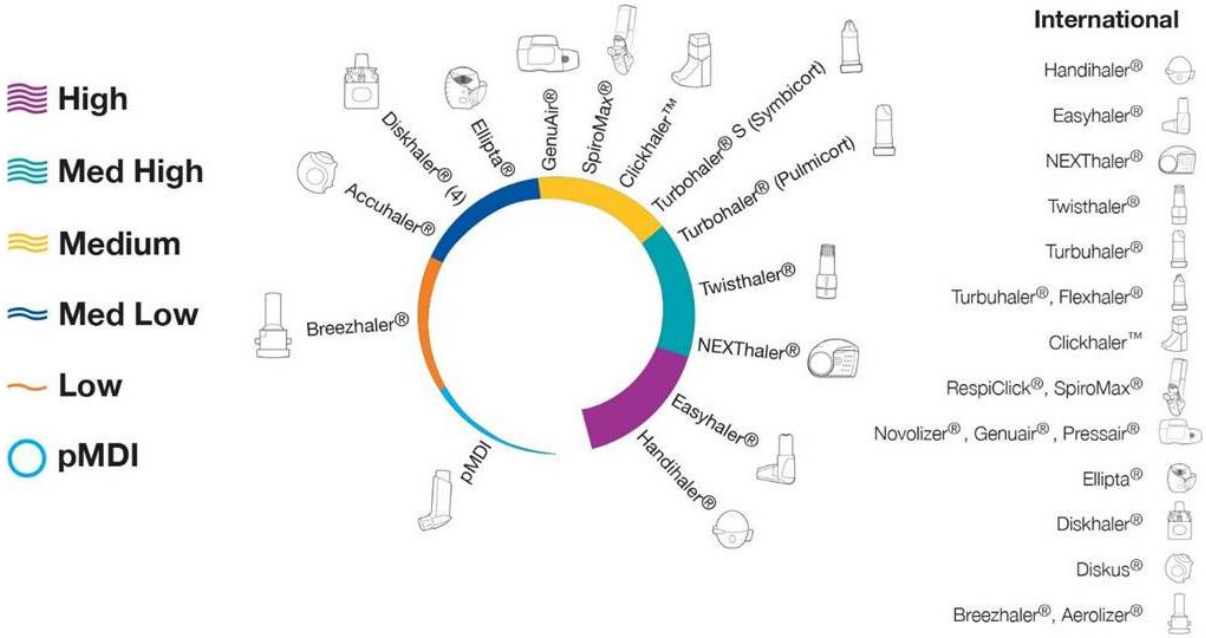
Required inspiratory flow rates for various inhalers



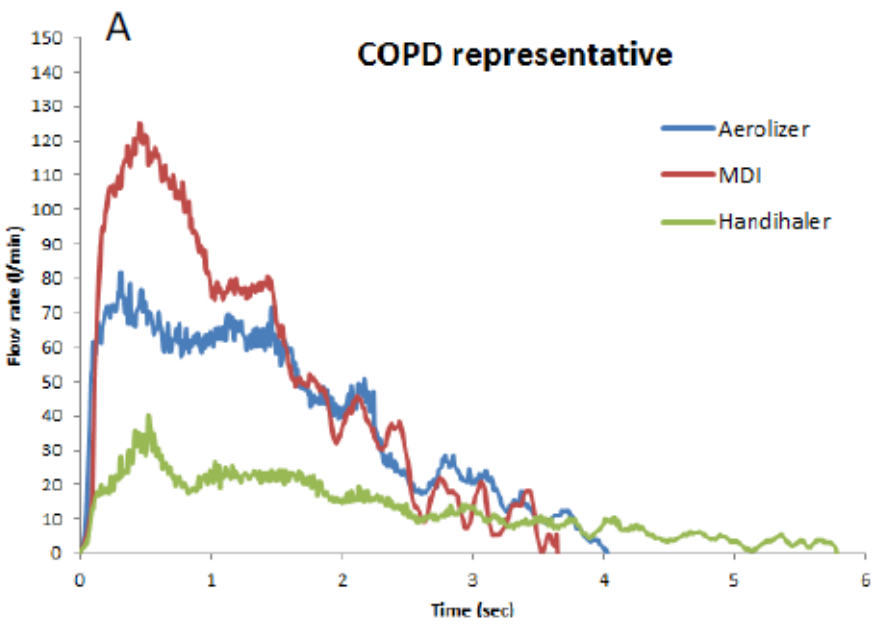
P. Haidl et al. Respiratory Medicine 2016;118:65-75

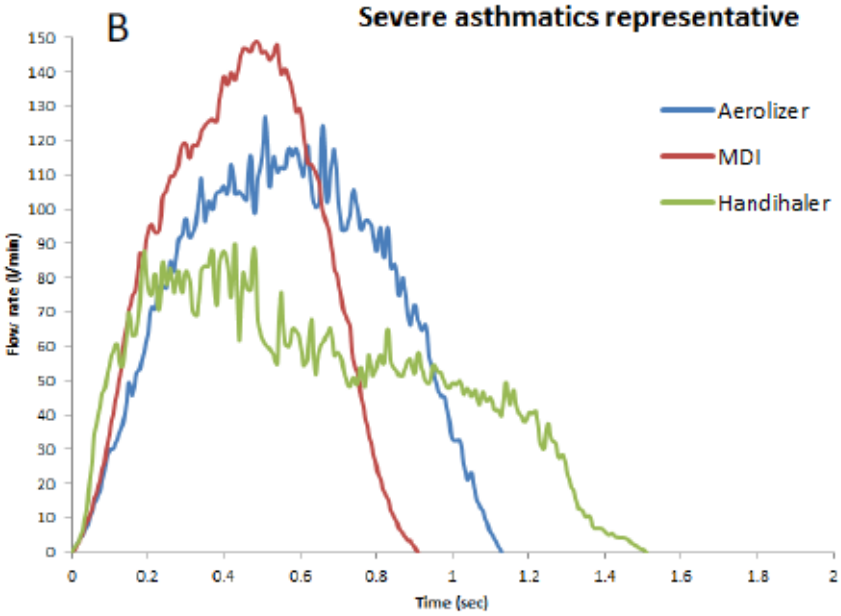
In check dial – inspiratory flow rate (L/min)





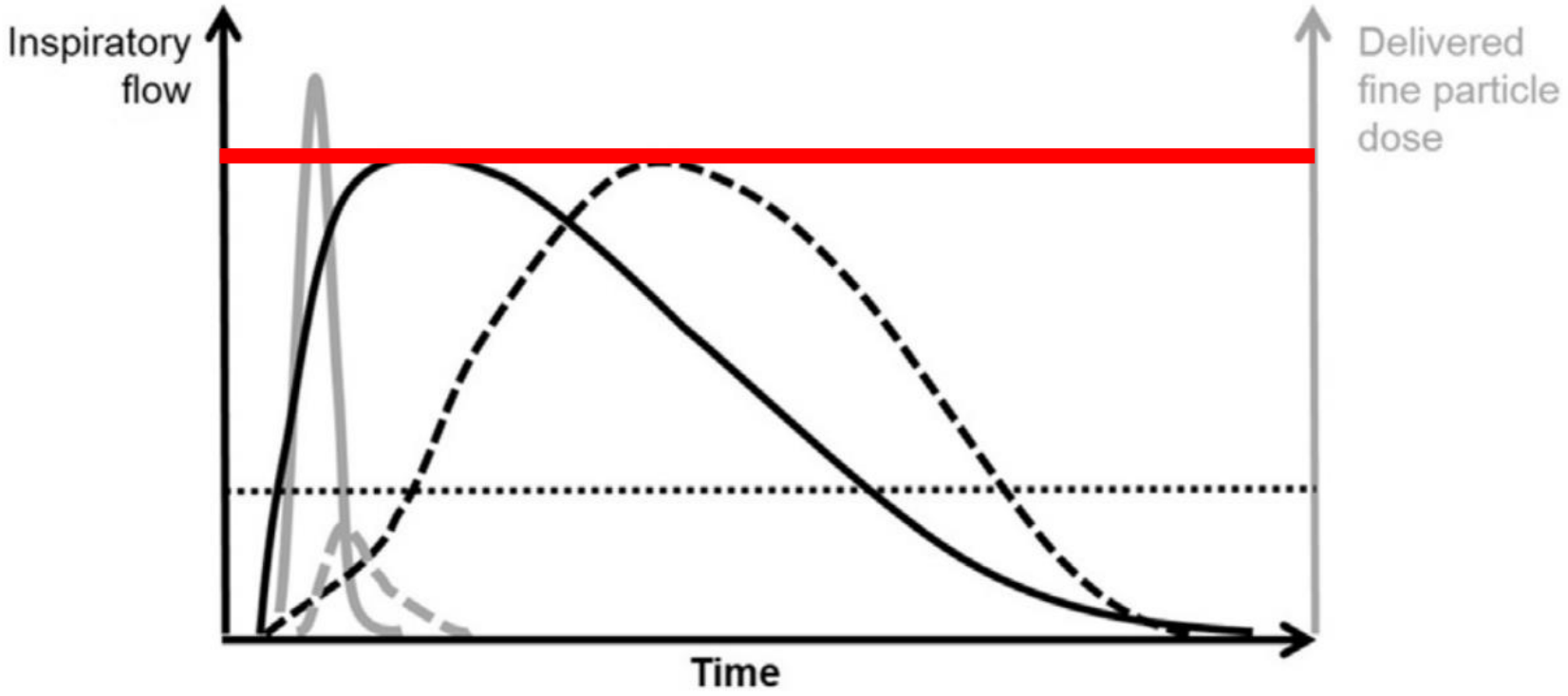
Inhalation Profiles in Patients with COPD and Asthma





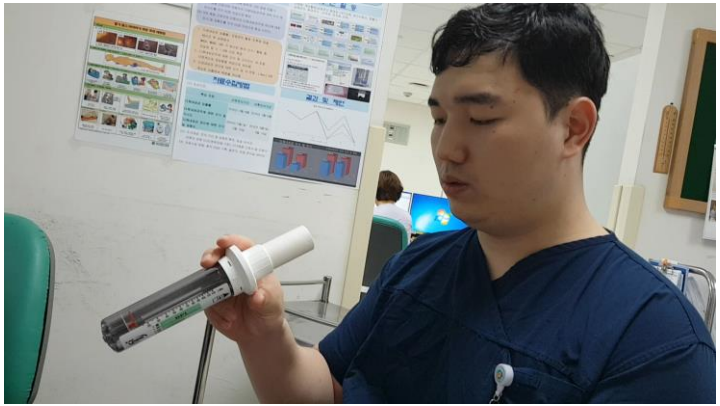
Parisini I, Usmani O, Murnane D, JOURNAL OF AEROSOL MEDICINE AND PULMONARY DRUG DELIVERY, 2015; 28: A15-A16

Forceful vs. Calm inhalation through DPI



P. Haidl et al. Respiratory Medicine 2016;118:65-75

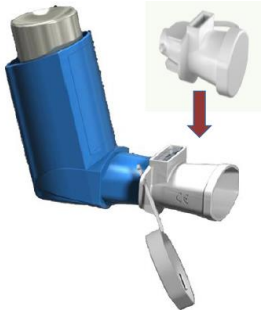
Too sufficient & forceful inspiratory flow



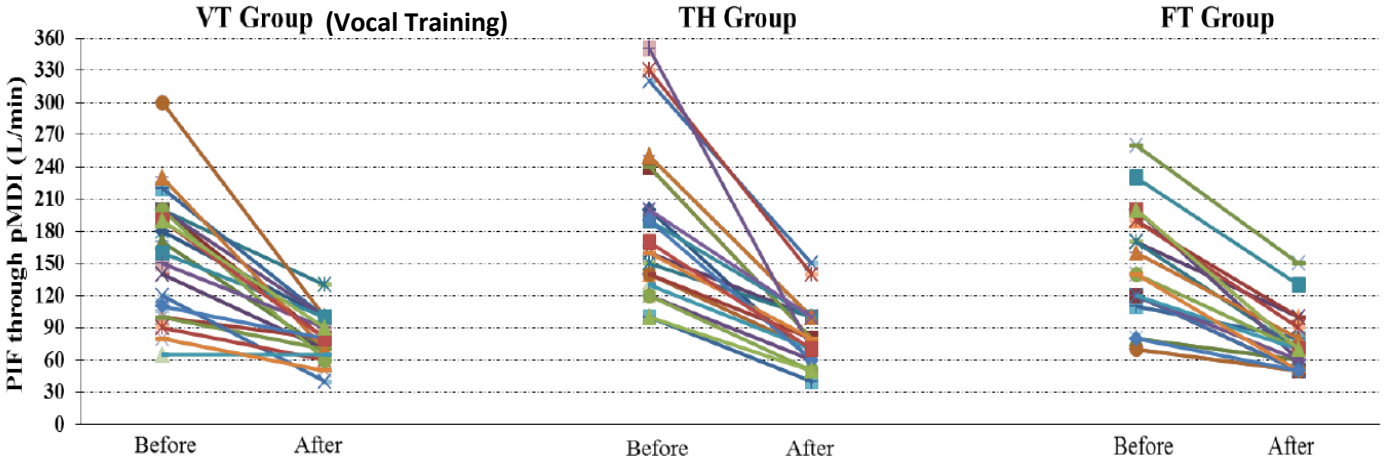
Optimization of pMDI Technique and Inhalation Flow

Trainhaler (TH)

CLEMENT CLARKE INTERNATIONAL



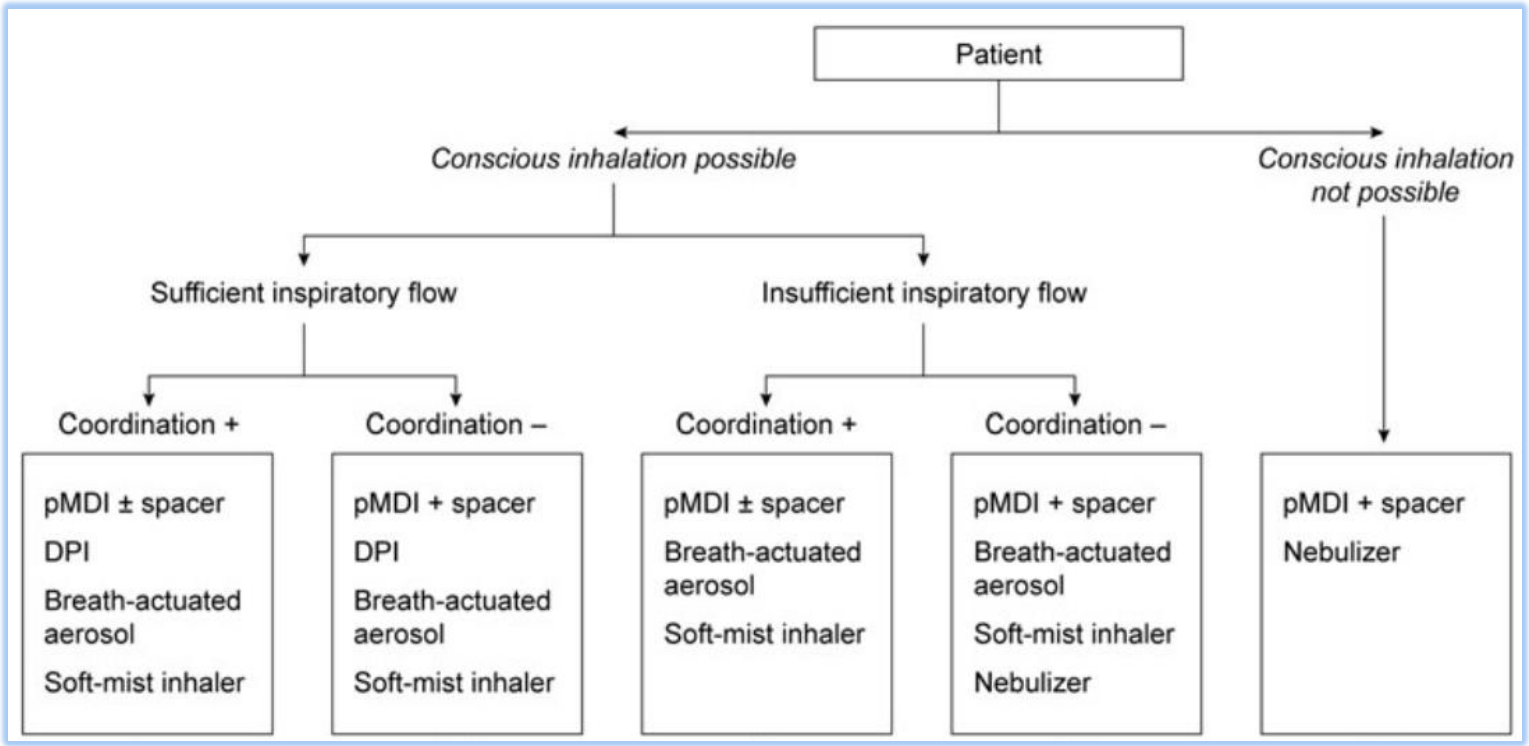
Flo-Tone (FT)



Ammari et al. ATS 2017 Conference, Washington, D.C.

Marginally sufficient inspiratory flow & calm breathing pattern

Choice of Delivery Device



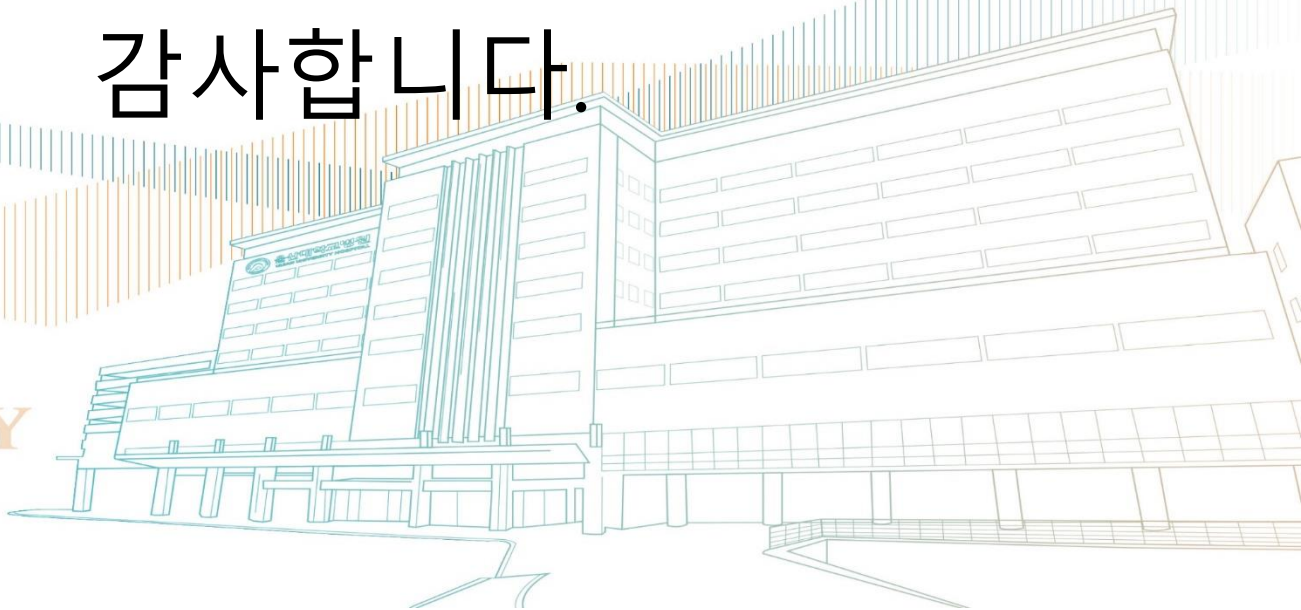
Dekhuijzen et al. Respir Med. 2013 Dec;107(12):1817-21

강의 요약

- Selecting inhaler devices is **personalized** medicine.
  - Patient's breathing patterns & preferences are different!
  - Device resistance에 따른 맞춤형 선택
    - ✓ **Low** resistance device – **Deeply** and **CALM** inhalation
    - ✓ **High** resistance device **– Deeply** and **FORCEFUL** inhalation
- DPI or pMDI technique and inhalation flow can be optimized
  - 사용법에 대한 환자 흡입제 교육과 지속적인 모니터링 중요!
- Inhalers have constantly been updated.

경청해 주셔서

감사합니다.



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