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A novel formulation technique for metered dose inhaler (MDI) suspensions

Hartwig Steckel*, Sebastian Wehle

Department of Pharmaceutics and Biopharmaceutics, Christian Albrecht University, Gutenbergstr. 76, 24118 Kiel, Germany

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Abstract

Metered dose inhalers (MDIs) are a widely used dosage form for pulmonary delivery of anti-asthmatic drugs. However, with the phase-out of chlorofluorocarbon (CFC) propellants and need to switch to the alternative pharmaceutically approved hydrofluoroalkane (HFA) propellants, the MDI formulator was faced with several technical challenges. Product components such as valves and elastomers needed to re-designed, and, due to the limited solubility of the commonly used surfactants in the HFA propellants, novel surfactants were developed or co-solvents were used to bring the conventional surfactants into solution. This paper describes a novel formulation approach for HFA based metered-dose inhalers. A physically stable micro-suspension of the model drug, budesonide, was formulated by an in situ-precipitation process using a hydrophilic stabilizer in the propellant system. A network-like structure of the precipitated drug and excipient was formed and resulted in physically stable suspensions in which the solid phase remained suspended in the propellant system for several weeks. Through life dose uniformity testing of MDI units containing formulations of budesonide produced by the novel process, was consistent and within the limits specified by the FDA draft guidance on metered dose inhalers. The fine particle fraction of the budesonide formulations showed a dependence on formulation composition and aerosol hardware (canister and actuator) illustrating flexibility in optimizing the product using this novel in situ formulation technique.
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Keywords: MDI; Propellants; Antiasthmatic drugs

1. Introduction

For the treatment of respiratory diseases metered dose inhalers (MDI) are a well-known dosage form. A MDI formulation consists of an active ingredient and one or more propellants. It may also contain formulation additives, such as surfactants and co-solvents. The propellant system is the main ingredient in MDI formulations and serves as a solvent and dispersion medium for drug substance and other excipients, and the energy source for generating the aerosol cloud on actuation while the dose is emitted from the metering

* Corresponding author. Tel.: +49 431 880 1333; fax: +49 431 880 1352.
E-mail address: steckel@pharmazie.uni-kiel.de (H. Steckel).

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valve (Williams et al., 1998). Due to the phase out of the ozone depleting chlorofluorocarbons (CFC), significant changes in the formulation approaches and MDI device components were necessary to address the different solvent properties of the new hydrofluoralkane (HFA) propellants (Purewal and Grant, 1998; Gonda, 2000). In a suspension based metered dose inhaler the density and the viscosity of the propellant system can influence the physical stability of the suspension. One approach to create a stable suspension is to utilize different compositions of the individual propellants in order to match the density of the suspended drug. The use of large porous or hollow particles is an alternative formulation principle to avoid creaming or caking of the particles in the propellant (Bowman and Greenleaf, 1999). Other authors report the formulation of a reverse water in fluorocarbon emulsion by the use of fluorinated surfactants in HFA 134a or HFA 227 (Butz et al., 2002). Techniques like spray drying, freeze-drying or co-grinding of the drug substances in combination with surface active ingredients are also well established methods for the preparation of MDIs in order to influence the physical properties of solid particles (Edwards et al., 1997; Keller, 1999). For aqueous systems, the controlled flocculation process is also a widely used technique to stabilize a suspended system. The goal is to alter the particle surface charge or to achieve particle separation via sterical hindrance using appropriate stabilizing excipients. Ranucci et al. proposed a controlled flocculation in CFC-MDIs in a two step procedure. The micro fine drug substance is first dispersed in a solution of oleic acid and lecithin in the low volatile propellant CFC 11. This suspension was weighed accurately into pressure resistant aerosol canisters and a valve was crimped onto the canister. Afterwards the propellant CFC 12 was added into the canister through the valve. A suspension with a flocculation volume of maximum 70% of the total propellant volume having a stability of 25 h was obtained (Ranucci et al., 1990).

The aim of this study was to establish a novel formulation technique for suspension metered dose inhalers by a controlled precipitation of the drug substance and excipients in the liquefied propellant system to obtain physically stable suspensions. The invention is based on a new preparation technique using hydroxypropyl-β-cyclodextrin (HP-β-CD), polyethylene glycol (PEG) and ethanol to stabilize the suspension. Both HP-β-CD and PEG are well-established pharmaceutical excipients and are approved for intravenous administration. Also, in vitro toxicity studies with human lung cell cultures indicate the safety of cyclodextrin derivatives for pulmonary use (Kinnarinen et al., 2004). The preparation starts with a real solution of drug substance and excipients in the aerosol container. After crimping the valve onto the container, a micro-fine suspension is formed spontaneously after addition of the propellant. Different types and concentrations of excipients were investigated on their influence on the physical stability of the suspension. In addition, the performance of MDI units containing the novel formulations were assessed by through-life dose content uniformity (DCU) and fine particle fraction (FPF) assessment.

2. Materials and methods

2.1. Materials

The propellant heptafluorpropane (HFA 227) was purchased from Solvay Flour and Derivate GmbH (Hannover, Germany). The propellant was filled using a Pamasol P 2016 filling station (Pamasol, Pfäffikon, Switzerland) into transparent glass containers without any inner coating (Glashüttenwerk Kipfenberg, Kipfenberg, Germany). Fifty microliters metering valves (type DF 30/50 RCU Delrin) and actuators type KN1 (orifice diameter of 0.7 mm) and IN 5 (orifice diameter of 0.5 mm) were obtained from Valois (Düsseldorf, Germany). As model drug budesonide, lot no. B09003 (Polfa S.A., Poznan, Poland) was used. Polyoxyethylenglykol (PEG) 300 (BASF AG, Ludwigshafen, Germany) and 99.9% dried ethanol (Merck KGaA, Darmstadt, Germany) were utilized as excipients. In addition, several cyclodextrins were screened for their potential use in the suspension system. All solvents for the analytical determinations were of HPLC grade (Merck KGaA, Darmstadt, Germany).

2.2. Methods

2.2.1. Preparation of the MDIs

A solution was prepared by mixing a native or a cyclodextrin derivate, PEG, the drug substance and dried ethanol. An aliquot was dispensed into an aerosol container. A 50 μl valve was immediately crimped onto each container and the canister was filled with HFA

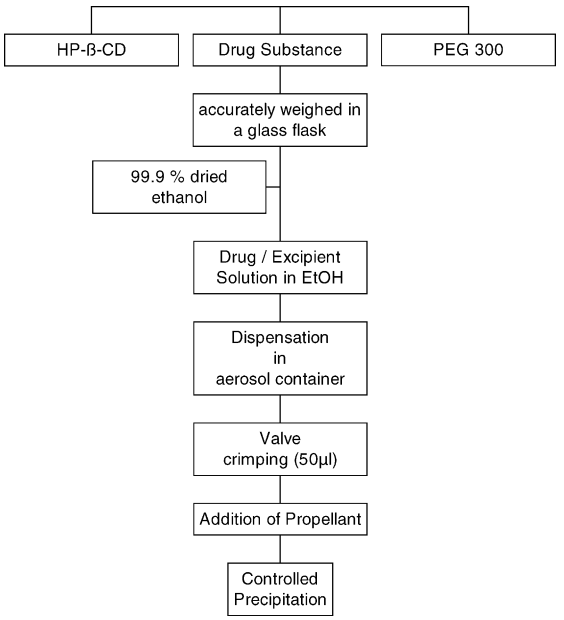

Fig. 1. Process flow chart for the preparation of the metered dose inhaler suspensions.

227 through the valve, as can be seen from the process flow chart in Fig. 1. The composition of a selection of budesonide formulations and the stabilizers investigated in the study are shown in Table 1. The concentration of budesonide was adjusted to 200 μg per shot. The concentration of dried ethanol was fixed to a maximum of 10.0% (w/w), to minimize the effect on the vapor pressure and consequently on the release velocity of the liquefied propellant throughout the orifice. A higher ethanol concentration would have also influenced the aerodynamic particle size distribution by a reduced de-aggregation of the suspension/propellant agglomerates.

2.2.2. *Aerodynamic particle size distribution*

The aerodynamic particle size distribution was assessed using a Multi Stage Liquid Impinger (MSLI), Apparatus C, Ph.Eur. Supp. 2001 (Ph.Eur., 2002). The flow rate was controlled with a flow meter type DFM (all equipment from ERWEKA GmbH, Heusenstamm, Germany). After assembly of the impinger, the filter stage was covered with a 53 mm diameter GF/A filter (Whatmann Int. Ltd., Maidstone, UK). All stages were filled with 20.0 ml of a mixture of 7.5 parts methanol and 2.5 parts double distilled water. Then the flow rate through the impinger was adjusted to 30 l/min. The induction port (USP metal throat) was connected with the mouthpiece of the metered dose inhaler with a rubber sealing. For each analysis, the MDI was shaken vigorously for 5 s and actuated to waste. This was repeated further four times. Afterwards, 10 consecutive doses (vigorous shaking in between) were released into the impinger. Then the induction port, mouthpiece and filter were carefully rinsed with an aliquot of a methanol/double distilled water mixture. The impinger itself was tightly sealed with Parafilm (Pechiney Plastic Packaging, Menasha, WI, USA) to avoid evaporation losses and gently shaken for 20 min to solubilize drug from the impinger stages. After dissolution of drug substance all fractions were analysed by HPLC. The evaluation of data was done according to the method

Table 1
The used cyclodextrin-types for the stabilization of the MDIs

CD-type	(mg)	PEG 300 (mg)	Ethanol (mg)	Budesonide (mg)	HFA 227 (g)	Solubility in PEG 300/ethanol	Characterisation after 227 addition
α-CD	55.3	200	1300	50	12.5	Insoluble	Sedimentation crystal growth
β-CD	64.6	200	1300	50	13.0	Insoluble	Coarse disperse crystal growth
γ-CD	73.8	200	1300	50	12.5	Insoluble	Sedimentation crystal growth
HP-α-CD	67.4	200	1300	50	12.6	Soluble	Fine-suspension
HP-β-CD	78.7	200	1300	50	12.7	Soluble	Fine-suspension
HP-γ-CD	89.9	200	1300	50	12.4	Soluble	Fine-suspension
2,6 Di-*o*-methyl-β-CD	75.7	200	1300	50	12.9	Soluble	Solution

Solubility behaviors of the excipients in PEG 300, anhydrous ethanol and the suspension characterization after 227 addition.

proposed in chapter 601, United States Pharmacopoeia (USP 26, 2003). The mass median aerodynamic diameter (MMAD) and the fine particle fraction (FPF) were calculated assuming a log-probability distribution of the aerosol spray. The FPF is defined as the percentage mass of the delivered drug dose smaller than 5 μm. This procedure was repeated twice ($n = 3$) for each of the produced formulations.

2.2.3. Dose content uniformity

For the dose content uniformity test a sampling apparatus according to Ph.Eur. was used. A glass fibre filter (Whatman Int. Ltd., Maidstone, UK) was used to collect the aerosol. The flow rate was adjusted at 28.3 l/min. The metered dose inhaler was connected to the dose uniformity sampling apparatus (DUSA). The aerosol canister was shaken prior to actuation. The first two shots were released to waste in order to prime the valve metering chamber. Afterwards one shot was released into the DUSA. The active substance that is deposited on the filter, the inner parts of the apparatus, the rubber sealing and the actuator was dissolved in 10.0 ml of a mixture of 7.5 parts methanol and 2.5 parts of double distilled water and, after dissolution, determined by HPLC. Doses were analyzed at the beginning (1–3), mid (98–101) and the end (198–200) of the calculated number of doses.

2.2.4. HPLC

The chromatographic system employed was an HPLC equipped with an autosampler (Type A 360, Kontron, Neufarn, Germany), a pump (Type 300, Gynkotec, München, Germany), a reversed phase column (LiChroChart® 125–4 mm, package material LiChrosorb® RP 18) and a UV detector (Type SPD6A, Techlab, Erkerode, Germany). For the integration of the detector-signal a Shimadzu C-R6A integrateor (Shimadzu Corp., Duisburg, Germany) was utilized. The mobile phase was a mixture of 47 parts methanol and 53 parts double distilled water (v/v). The mixture was degassed by ultrasonic treatment and afterwards used as eluent at a flow rate of 1.2 ml/min. The amount of budesonide was determined by UV detection at 254 nm. Calibration in a range of 1–20 μg/ml was done by using an external standard method.

2.2.5. Evaluation of the sedimentation behavior

To evaluate the suspension properties, the filled aerosol containers were inspected visually over a time period of at least 12 h after preparation. Digital photographs were taken (OLYMPUS AF1, Olympus, Hamburg, Germany) to document any tendency of the suspension to cream, to sediment or to detect crystal growth.

3. Results and discussion

Traditional preparation methods for manufacturing suspension MDIs involve an independent process step for micronization of the drug substance to a suitable particle size for pulmonary delivery. However, surfaces of mechanically micronized powders are not naturally grown as the crystal cleaves at the crystal face with the smallest attachment energy (Roberts et al., 1994). The micronization process using mills is described as extremely inefficient (Parrott, 1990) due to the high energy input which decreases crystallinity (Ogura and Sobue, 1970) and which can enhance chemical degradation. As a thermodynamically activated surface is created, the surface properties and thus the drug substance properties are altered (Ticehurst et al., 2000). The conversion of crystalline solid surfaces into partially amorphous solid surfaces leads to a “dynamic nature” of the micronized drug (Ward and Schultz, 1995). Thus, disordered structures in the material influence the performance in formulations (Buckton, 1997; Williams et al., 1999a,b). Accordingly, the influence of the particle shape and density, the presence of surfactants and the influence of suspension stabilizers such as α-lactose-monohydrate to avoid caking is well documented in the literature (Hettche and Engel, 1993). The aim of this work was to establish an in situ suspension preparation technique that starts from a solution of the drug substance in an ethanol co-solvent mixture, followed by controlled precipitation using the propellant as a non-solvent. Using this approach, milling of the drug is avoided and characterization of the physicochemical properties of the milled drug and the control of the particle size distribution, density, wettability, surface area, etc. becomes unnecessary.

During the pre-formulation phase it was most important to find suspension stabilizers which are soluble in ethanol and to select a co-solvent that interacts with

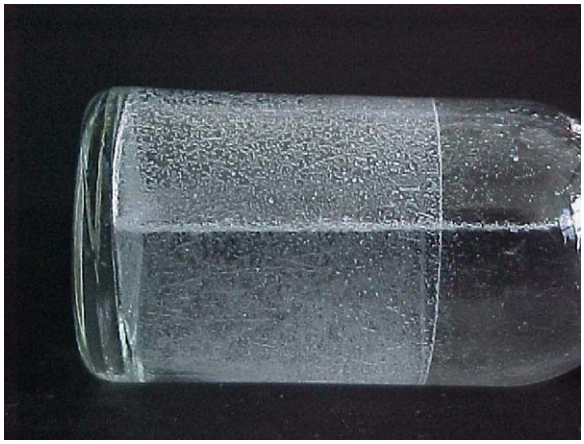

Fig. 2. Crystal-growth of budesonide in a solution MDI consisting of ethanol/PEG 300 and HFA 227 after a storage time of 10 days at room-temperature.

Fig. 3. Suspension MDIs containing HP-β-CD, PEG 300, ethanol and 200 μg budesonide/shot, 1 h after shaking. From left to right preparation number I, III, and V (see also Table 2).

the hydrophilic suspension stabilizer and the lipophilic propellant. In Table 1, some of the tested cyclodextrin types and the compositions of the prepared MDIs are shown. In this table, the solubility behavior of the cyclodextrins in ethanol/PEG 300 mixtures and the suspension characteristics after addition of the propellant to the solution are documented as well.

The native cyclodextrins, α-, β-, and γ-cyclodextrin are insoluble in ethanol/PEG 300. Therefore, the idea of precipitating the drug out of solution in the propellant could not be realized. However, these formulations were completed, but the formation of coarse suspensions that show caking on the bottom of the container and adsorption to the glass wall of the containers was observed. After storing the MDIs at room-temperature for 10 days, crystal-growth on the glass walls occurred. The same behavior was observed when no cyclodextrin was added to the drug solution: the addition of propellant to the clear solution of drug/PEG 300 and ethanol led to a supersaturated, instable solution where the budesonide starts to re-crystallize after 10 days storage at room temperature (Fig. 2).

In contrast to the native cyclodextrins, the modified cyclodextrins are freely soluble in the PEG/ethanol solvent system. The addition of the HFA propellant led to the formation of a milky and homogeneous suspension. A stable flocculated dispersion with a sediment volume equal to the total volume of the liquid propellant was obtained. In Fig. 3, three samples of different compositions of 200 μg/shot budesonide formulations are shown. The photograph was taken 1 h after shaking the MDIs.

The rapid precipitation of both, the drug and the cyclodextrin, in the non-solvent HFA 227 leads to very fine particles of the drug and the sugar derivative. It is assumed that the hydrophilic PEG rapidly covers the surface of both particulate ingredients and thereby reduces the interfacial energy between the propellant and the particles. The high sediment volume and the very good physical stability of the dispersion is explained by the cyclodextrin acting as a kind of bulking agent (Fig. 4) where the drug and the cyclodextrin form a network-like structure by non-covalent bonding, probably hydrogen bonds. After short-term storage (3 months at room temperature) the dispersions began slightly to cream but still were readily re-dispersible without any adsorption to the container walls and valve components to be observed. As the formulations containing HP-β-CD showed the most favorable suspension stability, it was used for further testing. The produced solutions containing DM-β-CD were not further analyzed this time, as the solution showed a high foaming effect due to the surface activity of this excipient.

For further studies, formulations with HP-β-CD and different concentrations of ethanol and PEG 300 were manufactured (Table 2) and characterized according to their sedimentation tendency, dosing properties and aerosolization behavior. Each of the formulations

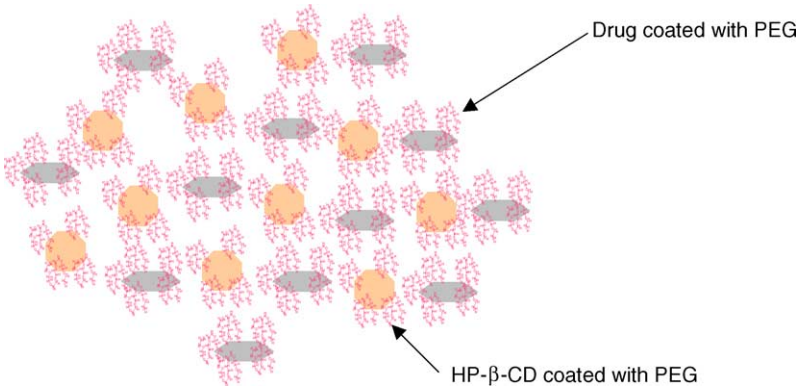

Fig. 4. Model of the particle formation and stabilization process by formation of a network-like structure.

Table 2
Compositions of 200 μg/shot budesonide formulations for DCU and impinger tests

	Product code					
	I	II	III	IV	V	VI*
HP-β-CD (mg)	83	83	26	68	26	68
Ethanol (mg)	300	880	880	1300	1000	1300
PEG 300 (mg)	1000	760	760	300	300	300
Budesonid (mg)	50	50	50	50	50	50
HFA 227 ad (g)	12.5	12.5	12.5	12.5	12.5	12.5

* Actuator type IN 5 with 0.5 mm o.d. was used.

contained 200 μg of budesonide. All formulations resulted in milky flocculated, stable suspensions with a low sedimentation tendency. This is also supported by the excellent content uniformity through container life of 200 doses performance as shown in Fig. 5. The dotted lines indicate the ±20%/±25% intervals of the target delivered dose of 200 μg/shot as defined in the current requirements by the FDA (Food and Drug Administration, 1998). The preparations show consistent dosing behavior with no obvious trend to an increase or decrease of single doses over the life of the container. No negative influence on valve function (i.e. as a result of valve clogging, return failure and drug deposition) was observed.

Fig. 6 shows the influence of the formulation composition on the fine particle fraction. The highest fine particle fraction resulted from compositions IV–VI with a value of approx. 16% for formulations VI and V and approx. 30% for formulation VI, expressed as percentage of delivered dose less than 5 μm. An increase in the PEG 300 content and decreasing ethanol content reduced the FPF to 6.4% as would be expected due to the increased level of the non-volatile compound PEG 300 (composition I). The MMAD values behave inversely to the FPF, composition I having a MMAD of 7.8 μm that decreases to 4.0 μm for composition V. In addition,

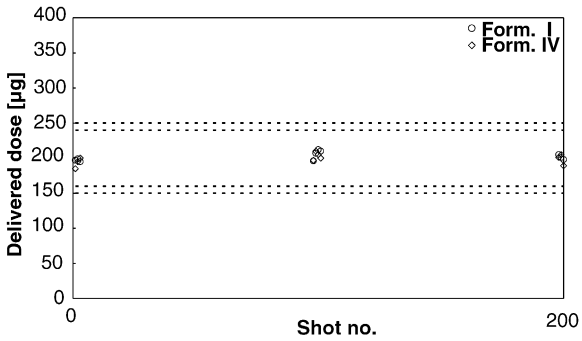

Fig. 5. DCU-test for 200 μg/shot budesonide formulations I and IV (Table 2).

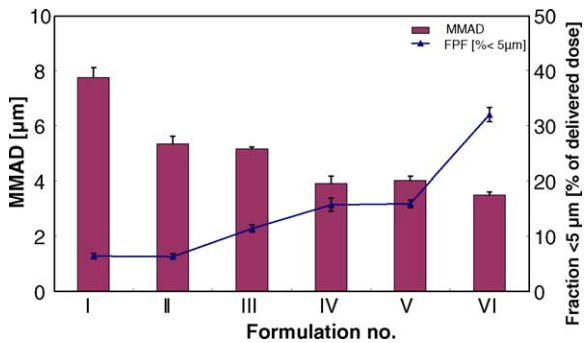

Fig. 6. MMAD and FPF [percentage of delivered dose <5 μm] of the five investigated budesonide MDIs (n = 3, error bars = S.D.).

a relationship between the composition of the investigated MDIs and the resulting FPF could be observed. Comparing the compositions II and III indicates that the concentration of HP-β-CD does slightly affect the FPF towards higher fine particle fractions with lower solid content. Surprisingly, the highest ethanol content led to the highest FPF (comparing formulations IV and V) which only can be explained by a decreased spray velocity of the released aerosol plume. This in turn leads less deposition in the upper impactor stages and facilitates particle shrinkage due to solvent evaporation. However, as the influence of the co-solvent system on budesonide solubility has not been analyzed, further studies are necessary to investigate the influence of formulation variables on the aerosol performance.

The fine particle fraction of formulation IV increased when tested with an actuator with a smaller orifice diameter (VI), illustrating the importance of device selection in optimizing MDI performance.

4. Conclusion

A novel two-step precipitation process, which involves the use of HP-β-CD, PEG 300 and ethanol, has been described to produce physically stable MDI suspensions. Due to the hydrophilic character of the solution and the lipophilicity of the propellant 227, a rapid precipitation of the dissolved drug takes place. The test drug substance budesonide is soluble in the investigated amounts of PEG 300, ethanol and HP-β-CD. After the addition of the propellant a milky suspension resulted which remained stable for 3 months. During storage of >3 months no tendency of agglomeration or sedimentation of the suspension could be observed. In the absence of HP-β-CD, a supersaturated solution formed which re-crystallized at the container inner surfaces upon storage. The dose content uniformity of aerosol units containing budesonide formulations produced with the novel process, were consistent throughout the unit life of 200 doses. The corresponding FPFs ranged approximately between 6 and 30% of the delivered dose, depending upon the formulation composition and actuator used. Thus, modulation of the MDI efficiency is possible through further optimization of the formulation and device.

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