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Short Communication

Involvement of pH and Internal Surface of Cans on the Budesonide Solution Stability in HFA Metered Dose Inhaler

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ABSTRACT

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with the time under the influence of a variety of environmental factors such as temperature, humidity, pH and light, and to establish a retest period for the drug substance or a shelf life for the drug product and recommended storage conditions. Due to high lipophilicity of budesonide, it is not possible to prepare simple solution having the desired concentration of this drug without using co-solvent. Aim of this study was to compare the stability of budesonide at different canisters (standard aluminium, anodized aluminium direct surface modification (DSM) and fluorocarbon polymer (FCP) and pH values. Two type of formulation without and with acid were prepared to evaluate the effect of pH on stability of budesonide solution in anodized aluminium, DSM and FCP cans. After addition of strong acid, under accelerated stability conditions, only a slight decrease in the assay is observed after six months. In this study the best results have been obtained with anodized aluminium cans and solution with a pH of 3.5.

Keywords: Budesonide ; stability; HFA-metered dose inhaler; pH; canister.

INTRODUCTION

Budesonide is a synthetic glucocorticoid with high lipophilicity and mainly anti-inflammatory activity which acts via inhibiting broncho constrictor mechanisms and decreasing hyperresponsiveness[1,2].The pressurized-metered dose inhalers (pMDI) are most widely used advice for delivering a drug into the airway. Since the pMDIs directly targets drugs to lungs, they offer advantages of bypassing the first pass metabolism, reducing the dosage frequency and minimizing side effects. The key components of the pMDI are the canister, propellant, concentrated drug formulation, metering valve and actuator which all play roles in the formation of the aerosol cloud and delivery efficiency[2,3]. Chlorofluorocarbons (CFCs) were previously the most commonly used propellants in pMDIs, but their production has been prohibited due to CFCs causing ozone (O_3) layer depletion in the atmosphere and replaced by hydrofluoroalkanes (HFAs) as propellant for use with pharmaceutical aerosol delivered in pMDIs[1]. The physicochemical properties of HFAs are different from CFCs and they do not damage the ozone layer [2,3]. Reformulation of pMDIs with HFAs can be developed in either a solution or suspension system. Solution system offer the advantage of being homogenous with the active ingredient and excipients completely dissolved in the propellant vehicle or its mixture with suitable co-solvents such as ethanol [4]. Because of high lipophilicity, budesonide is virtually insoluble in water but is readily soluble in alcohols. However the alcoholic solutions have too little stability for pharmaceutical use because large amounts of budesonide decompose within a short time. It has been found that the stability of budesonide containing solutions depends on the pH, so that the stability of the solutions increases as the pH decrease [5]. For pharmaceutical use of budesonide as pMDI, enema or rectal foam the suggested preferred pH values has been 3-3.5 [4,6]. Any pharmaceutically acceptable organic acid (like

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citric acid, tartaric acid) and inorganic acid (like hydrochloric acid, phosphoric acid) can be used to adjust the pH [5]. The aim of this study was to consider the stability of budesonide solution at different formulation of HFA metered dose inhaler at low pH and using different canisters.

MATERIALS AND METHODS

Micronized budesonide and HFA 134a were obtained from Farmabios and Mexicheman companies respectively. Anhydrous ethanol, glycerol and hyrochloric acid were purchased from Merck local supplier in Iran. Cans and valves were purchased from Presspart and Bespak companies respectively. All chemicals were analytical grade.

Experimental design: The budesonide inhaler was designed as a stable pharmaceutical solution consist of active ingredient, co-solvent and low volatility component in a HFA 134a propellant. Two type of formulation without and with acid were prepared to evaluate the effect of pH on stability of budesonide solution. The composition of formulation 1 was: 0.36% (w/w) budesonide, 13% (w/w) ethanol, 1.3% (w/w) glycerol in HFA 134a to 12 ml/can which was distributed in aluminum cans. The composition of formulation 2 was**:** 0.36% (w/w) budesonide, 13% (w/w) ethanol, 1.3% (w/w) glycerol and aliqouts of 1.0 M hydrochloric acid to obtain pH 3.5 in HFA 134a to 12 ml/can which was distributed in anodised aluminium, direct surface modification (DSM) and fluorocarbon polymer (FCP) cans.

Preparation of the pMDIs: The pMDIs were prepared by the pressure filling method. The glycerol was dispersed in anhydrous ethanol. The micronized budesonide was added and mixed by Silverson L4RT homogenizer until dissolved. Hydrochloric acid was added to type 2 formulation to obtain the clear solution with pH 3. 5. Each aliquot was filled into cans. Then 50 µl metering valves were crimp-sealed on to the cans and they filled with propellant HFA 134a. All cans were stored at 40ºC and 75% humidity for 6 months.

Anlaysis of budesonide pMDI formulations: Budesonide was analysed by Waters Alliance HPLC system equipped with a Waters 2695 pump, plus an auto-sampler and a 2487 UV detector which was operated at 240 nm. The stainless steel column 150 × 4.6 mm, 3 µm, ODS2 were used in this study. The assay of active ingredient mobile phase consisted of phosphate buffer 25 mM pH 3.2, acetonitril and ethanol in the ratio of 66:34:2 (V/V) at a flow rate of 1.5 ml/min. The mobile phase of related substances test was: mobile phase A (2 volumes of ethanol, 34 volumes of acetonitril and 66 volumes of phosphate buffer pH 3.2), mobile phase B (1 volume of acetonitril and 1 volume of phosphate buffer pH 3.2). The flow rate was 1 ml/min. The injection volumes were 20 and 100µl for assay and related substances respectively. The column temperature was 50ºC. The chromatograph was programmed as follows:

Time (Minutes)	Mobile phase A (%V/V)	Mobile phase B (%V/V)	Comment
0-38	100	0	Isocratic
38-50	100→0	0→100	Linear gradient
50-60	0	100	Isocratic
60-61	0→100	100→0	Linear gradient
61-70	100	0	Re-equilibration

Content of budesonide delivered by actuation of the valve: The content of the active ingredient delivered by actuation of the valve was determined by delivering 10 successive actuation of the valve after priming through the central hole of a stainless steel with three legs that was placed in a suitable vessel including 32 ml of acetonitrile. The inhaler was discharged in the inverted position under the surface of the solvent. The solution and washings obtained from the set of 10 actuations was transferred to a flask and diluted to volume with appropriate amounts of acetonitrile and phosphate buffer solution pH 3.2. The final solution contained 0.01% W/V budesonide in a mixture of 34 volumes of acetonitrile and 66 volumes of phosphate buffer pH 3.2. The result was calculated as the amount of active ingredient from each actuation of the valve (BP, 2012).

Assessment of related substances: Solution (1): the container was discharged into a small, dry vessel to obtain 1 mg of budesonide and dissolved the residue in 3.4 ml of acetonitrile. The solution was mixed by aid of ultrasound and added sufficient phosphate buffer pH 3.2 to produce 10 ml and filtered. Solution (2): 1 volume of Solution (1) was diluted to 200 volumes with diluent solution. Solution (3): 1 volume of Solution (2) was diluted to 10 volumes with diluent solution. Diluent solution: A mixture of 34 volumes of acetonitrile and 66 volumes of phosphate buffer pH 3.2 (BP, 2012).

Statistical analysis: All data are presented as mean ± standard deviation (SD). Statistical analysis was done using student´s t-test. P-value < 0.05 was

considered significant statistically. Calculation were performed using SPSS version 11.5.

RESULTS AND DISCUSSION

One of most common method for characterization of stability for a drug involves preparing solutions under various " stressing" conditions such as accelerated conditions and low and high pH. The solution are analysed via HPLC to determined the levels of degradation over time [2,3]. The contents of budesonide (delivered by actuation of the valve) and related substances in formulation 1 and 2 have been shown in Tables 1, 2, 3, 4. For formulation 1 the amount of budesonide was 90.56 ± 1.06 after 6 months compared with initial amount 105.33 ± 1.07 which indicate that the amount of budesonide tends to decrease in the aluminum canister (Table 1). Related substances test also confirmed instability of budesonide compared with initial content in this formulation (Table 1) The content of budesonide (delivered by actuation of the valve) in formulation 2, in anodized canister was not associated with a significant decrease compared with initial amount (109.57 ± 0.66 *V* 109.66 ± 1.07) . In the case of related substances test, as shown in Table 2 the total impurities in anodized can (0.30 ± 0.13) was lower as compared with aluminium can (4.93 ± 1.00). The amount of budesonide in formulation 2 after 6 month in DSM can (109.03± 1.05) and FCP can (109.02 ± 1.03) were not associated with a significant decrease compared with their initial amounts (109.3 ± 1.32 and 110.06 ± 1.15) respectively. In the case of related substance , the total impurities after 6 month in DSM and FCP cans were 2.73 ± 0.50 and 2.56 ± 0.50 respectively as compared with aluminium can 4.93 ± 1.00 (Tables 3,4). Although the instability of budesonide in formulation 2 in all different internal surface of cans were not significant compared with formulation 1 but only formulation 2 in anodized can was satisfied with BP standard for related substance (not more than 0.5% for any impurities and not more than 1.5 % for total impurities) British Pharmacopeia standard was satisfied with formulation 2 in anodized cans. In conclusion our results showed that budesonide is more stable in solution with a pH of 3.5 and anodized aluminium canisters compared with DSM and FCP cans.

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CONFLICT OF INTERES

We declare that we have no conflict of interest.

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Table 1. Stability of budesonide in formulation 1 without acid in aluminium can . Values are expressed as mean ± SD (n=3)

Tests	Period of storage				
	Initial	One month	Two months	Three months	Six months
Content of budesonide (%)	105.33 ± 1.07	104.06 ± 1.00	103 ± 0.91	101.05 ± 1.01	90.56 ± 1.06
Related substances (%)					
Largest impurity	0.181 ± 0.06	0.59 ± 0.07	0.87 ± 0.10	0.91 ± 0.09	1.99 ± 0.10
Total impurities	0.45 ± 0.06	0.95 ± 0.05	1.49 ± 0.08	2.57 ± 0.24	4.93 ± 1.00

Table 2: Stability of budesonide in formulation 2 with a pH of 3.5 in anodized can. Values are expressed as mean ± SD (n=3)

Tests	Period of storage				
	Initial	One month	Two months	Three months	Six months
Content of budesonide (%)	109.57 ± 0.66	109.23 ± 1.02	108.36 ± 0.73	108.76 ± 0.98	109.66 ± 1.07#
Related substances Largest impurity Total impurities	 0.13 ± 0.05 0.20 ± 0.08	 0.24 ± 0.05 0.21 ± 0.04	 0.19 ± 0.06 0.26 ± 0.07	 0.21 ± 0.07 0.28 ± 0.02	 0.26 ± 0.02 0.30 ± 0.13***

p<0.0001# , significantly different from aluminium can.
p< 0.005 ***, significantly different from aluminium can.

Table 3: Stability of budesonide in formulation 2 with a pH of 3.5 in DSM can . Values are expressed as mean ± SD (n=3)

Tests	Period of storage				
	Initial	One month	Two months	Three months	Six months
Content of budesonide (%)	109.3 ± 1.32	108.46 ± 1.02	108.66 ± 1.95	109.167 ± 0.37	109.03 ± 1.05#
Related substances Largest impurity Total impurities	 0.15 ± 0.07 0.38 ± 0.06	 0.27 ± 0.07 0.92 ± 0.07	 0.43 ± 0.05 1.29 ± 0.05	 0.65 ± 0.06 2.30 ± 0.10	 0.81 ± 0.05 2.73 ± 0.50*

p<0.0001# , significantly different from aluminium can.
p< 0.05 *, significantly different from aluminium can.

Table 4: Stability of budesonide in formulation 2 with a pH of 3.5 in FCP can. Values are expressed as mean ± SD (n=3)

Tests	Period of storage				
	Initial	One month	Two months	Three months	Six months
Content of budesonide (%)	110.06 ± 1.15	109.03 ± 1.25	108.47 ± 1.05	107.2 ± 0.90	109.02 ± 1.03#
Related substances Largest impurity Total impurities	 0.12 ± 0.03 0.21 ± 0.07	 0.29 ± 0.05 0.32 ± 0.03	 0.29 ± 0.05 0.61 ± 0.03	 0.4 ± 0.04 1.33 ± 0.20	 0.43 ± 0.04 2.56 ± 0.50**

p<0.0001# , significantly different from aluminium can.
p< 0.025 **, significantly different from aluminium can.