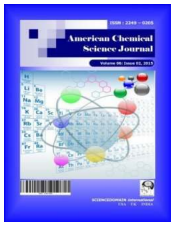


American Chemical Science Journal
13(1): 1-7, 2016, Article no.ACSJ.24107
ISSN: 2249-0205

SCIENCEDOMAIN *international*
www.sciencedomain.org

Evaluation of the Interaction of Micronized Salbutamol Sulphate Particles with a Polymer Surface

Raed A. Ghanem[1*] and Abdel-Aziz Matani[2]

[1]Department of Chemistry, University of Al al-Bayt, P.O.Box 130040, Mafraq 25113, Jordan.
[2]Department of Radiological Sciences, University of Dammam, Saudi Arabia.

Authors' contributions

This work was carried out in collaboration between both authors. Both authors are equally contributed to run this study. Both authors read and approved the final manuscript.

Article Information

DOI: 10.9734/ACSJ/2016/24107
Editor(s):
(1) Ho Soon Min, Department of Chemistry, Faculty of Science, INTI International University, Malaysia.
Reviewers:
(1) Hao Wang, Northeastern University, Liaoning, China.
(2) M. Mohan Varma, Shri Vishnu College of Pharmacy, India.
Complete Peer review History: http://sciencedomain.org/review-history/13284

Original Research Article

Received 4th January 2016
Accepted 1st February 2016
Published 12th February 2016

ABSTRACT

The interaction between micronized Salbutamol Sulphate molecules and the internal surface of the constant volume chamber of a Metered Dose Inhaler (MDI) were studied using Chromatographic methods, a Scanning Electron Microscope (SEM) and Spectroscopic methods. The extensive usage of the MDI to deliver the micronized Salbutamol Sulpate results in the systematic decrease of both the shot weight and the concentration of delivered drug, as the number of the actuations increases. Micronized Salbutamol Sulphate particles were attached onto the internal surface as single crystals and layers of the drug particles. Spectroscopic analysis of the attached particle confirms that it is Salbutamol Sulphate and that there are no new bands disappearing or arising as a result of the interaction between drug molecules and the internal surface, which indicates that this interaction is Physisorption.

Keywords: Salbutamol sulphate; metered dose inhaler; drug interaction; phsisorption.

**Corresponding author: E-mail: raedag@aabu.edu.jo;*

1. INTRODUCTION

Salbutamol {2-(tert-butylamino)-1-(4-(hydroxy-3-hydroxymethyl-phenyl) ethanol} (Fig. 1) is a drug with β2-adrenoceptor activities and is used for the treatment of asthma and breathing problems [1-3]. It is normally delivered to the patients as inhaled suspension using a Metered Dose Inhaler (MDI). Various polymer materials (i.e. polyester and poly acetal) are used in the manufacturing of different parts of MDI [4].

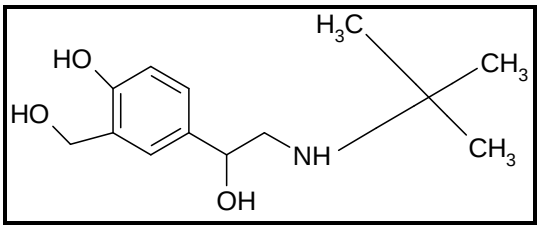


Fig. 1. The chemical structure of Salbutamol Sulphate

Most of these polymers have polar centers, and as it could be expected, in the presence polar drug molecules, such as micronised Salbutamol Sulphate the interaction between the polar center of polymer and polar drug species is expected [4,5]. Literature contains few works on the nature of the interaction of micronised Salbutamol Sulphate particles crystals with polymer surfaces.

A MDI is a device widely used in the managed treatment of asthma. They contain the active drug Salbutamol Sulphate dissolved or suspended in a propellant. The inhaler consists of a storage canister containing the drug/ propellant mixtures, and a connected metering valve. They are pressurized, hand-held inhalers that use propellants to deliver a specific amount of medication to the lungs of a patient [4,5]. The metered chamber in the valve is responsible for providing a precisely measured volume of the drug/ propellant mixture resulting in an accurate dose of medication with every actuation. In operation, the controlled volume of the mixture is displaced from the constant volume chamber of the valve and is inhaled by the patient. A return actuation refills the constant volume chamber and releases the metered drug mixture through the recipient's respiratory system. During the entire life cycle of the device, the drug mixture remains in contact with the inner surface of the storage canister as well as the metering chamber. The mixture inside the constant volume chamber is, thereby, displaced and replaced at variable times. The construction of the constant volume chamber as well as the valve consists of a number of polymers including polyester and polyacetal.

Due to nature of material used in the manufacturing of the MDI device (chloroflourocarbone and hydroflouroalkane) a decrease in the delivered drug is expected due to the irreversible adhesion of the drug particles to internal surface of the polymer surface, it was reported that an increase in the adhesion force decrease the emitted dose [6,7]. The interaction between micronized particulates and internal surface may be possible to predict from thermodynamics considerations of the surface free energy measurements through using the atomic force microscopy [8]. The aim of this study is to investigate the type and factors affecting the interaction between the micronized salbutamol material and the internal surface of the MDI device.

2. EXPERIMENTAL METHODS

To achieve the main objective of this study both the concentrations of Salbutamol Sulphate per actuation as well as the weight of the pack valve were recorded. The concentration of drug per actuation was analyzed using the proposed validated analytical methods. The average amount of the delivered Salbutamol was expressed as (wt/wt %). Also, the average amount of the drug deposited on the actuator was detected, collected and investigated using Scanning Electron Microscope (SEM). IR spectra were recorded on an FT-IR Jasco 300E instrument in the 190–600 cm^{-1} range using either Nujol mulls supported between polyethylene plates or KBr pellets.

2.1 Materials

Salbutamol Sulphate ($C_{13}H_{21}NO_3$) was obtained from sigma Aldrich and was used as received without further purification.

2.2 Chromatographic System

A water mode 600 solvent delivery system was used together with a Water Nova-pak, C18 and 3.9 x 150 mm column packed with (3.9 µm particle size). Samples were injected using a Rheodyne injector with 20 µl sample loop. Detection was done with UV/VIS diode array detector (Water PD 900) Absorbance Detector

operating at 220 nm, with an AUFS of 0.11. Peak evolution and quantization were made using Water Millennium software. The mobile phase consisted of 35% v/v methanol/water and flow Rate of 1.0 ml/min.

2.3 Stimulated Use Test

This test was implemented in order to study how the use of the MDI affects the deposition of Salbutamol particles on the polymer surface of the metering chamber [9]. Single actuations were discharged at each time and collected for later analysis. The inhalers were stored horizontally at 25℃. The procedure includes weighing of the pack valve down before and after the substance's discharge. The collected/ delivered dose was assayed. The test was performed based on the number of actuations (200 actuations) mentioned in the label.

3. RESULTS AND DISCUSSION

3.1 Evaluation of the Analytical Method

The main purpose of this study is to investigate the interaction between Salbutamol Sulphate molecules and the internal polymer surface of the using a validated analytical method. Fig. 2 shows the typical chromatogram of the standard Salbutamol Sulphate. It shows that the Salbutamol Sulphate appears at around 5.4 minutes. A set of calibration standards solutions containing Salbutamol were prepared (150 to 2000 µg/ml) and analyzed. The chromatographic data produced are graphically presented in Fig. 2 (see inserted figure top-right). The calibration curve was found to follow a linear relationship and from the calibration experiments, the smallest concentration of Salbutamol Sulphate that can be detected is estimated to be 150 µg/ml. The described analytical method was used to analyze a real sample of some commercial samples containing Salbutamol Sulphate and the content of the delivered drug per actuation. A good agreement was found in respect to the label claim for the analyzed samples, as it was found to be within the confidence ranges commonly accepted (i.e. < 4%).

These results show the possible applicability of the proposed method to serve the purpose of our study, without possible interference problems derived from other substances which frequently appear in such formulations. The proposed method was compared with another analytical method applied to the same set of samples. The comparison between the two methods show that there are no significant differences in the results obtained from both methods, however our method is faster and easier to apply [10-15].

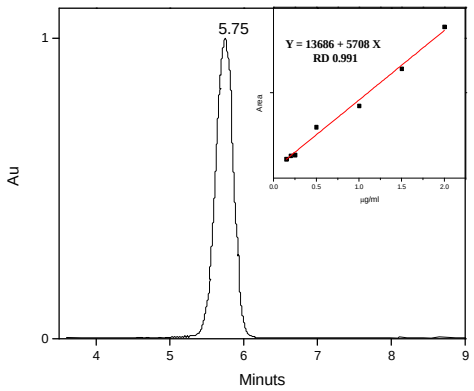


Fig. 2. The chromatogram of Salbutamol Sulphate. The inserted figure is for the calibration curve

3.2 Metered Dose Inhaler (MDI) Performance

Micronised Salbutamol Sulphate is normally delivered to the patients through MDI as an inhaled suspensions formulation. A stimulated use test was implemented, in order to study how the use of the MDI affects the deposition of Salbutamol Sulphate particles on the polymer surface of the metering chamber, and therefore how it affects the concentration of the delivered drug concentration. Fig. 3 shows how the shot weight varies over the actuation number for different MDI samples from different inhalers. From the obtained results, it is appearing that none of the tested MDI devices have consistency in their shot weights. This means, that for all tested devices the shot weight per actuation is not reproducible and varies from one device to another and from one actuation to another. Fig. 4A, clearly shows the weight distribution of the delivered drug over 200 actuations. It was found that the shot weight oscillates around an overall average value of 67.5 mg and the weight of 72.5% of shots fits in the range of 62.5 mg and 77.5 mg. The fluctuation of the shots weight and the negative deviation from the claimed delivered shot weight (100 mg) could be attributed to; the possible influence from temperature fluctuation during the test, a leakage and drain back into the storage canister due to a longer rest time, shaking of the sample which maybe results in

partial release of drug mixture from the constant volume chamber and/ or to a possible deposition of the drug molecules onto the internal surface.

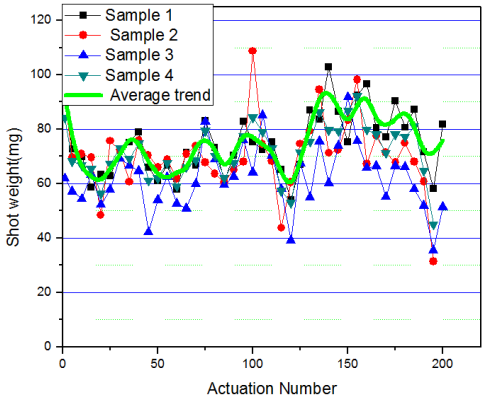


Fig. 3. Plot of the delivered drug mass (mg) versus actuation numbers of different samples. The smoothed line shows the general trend of the variation of the mass of delivered drug as actuations number increases

As we reported in the experimental Section, the delivered drug per actuation was collected for further analysis to determine their Salbutamol Sulphate contents. The variation of the average concentration of the delivered drug versus the actuation number was graphically represented in Fig. 5. In general, the concentration of Salbutamol Sulphate decreases as the actuation number increases. In fact, the concentration starts to stabilize after 30 actuations, the concentration of Salbutamol Sulphate per shot weight (wt/wt %) was found to oscillate around an overall average value of 95% where 63.4% of the shots (Fig. 4B) exists in the range between 95% to 105%. Also the concentration of the delivered drug is lower than the claimed concentration (100 mg of Salbutamol Sulphate per actuation). Fig. 4C shows the 3D plot of the shot weight (mg) versus the actuation number and concentrations of the delivered drug (wt/wt %).

3.3 Drug-polymer Interaction

Results obtained from the stimulated use test, shows that there is a loss of concentration of the drug, which is found to be directly proportional to the extensive use of the inhaler. The decrease in the dosage concentration is attributed to the deposition of the Salbutamol Sulphate on the internal surface of the constant volume metered chamber. Deposition of Salbutamol Sulphate molecules were investigated through studying the modification of the internal surface of the constant volume metered chamber in the inhaler. Molecules deposition inside the chamber was studied after number of actuations.

SEM was used to investigate the possibility of the deposition of drug particles onto the polymer surface following the procedure of the stimulated use test of the MDI device. Results from SEM revealed that Salbutamol Sulphate starts to accumulate onto the internal surface after a few number of actuations where drug particles and

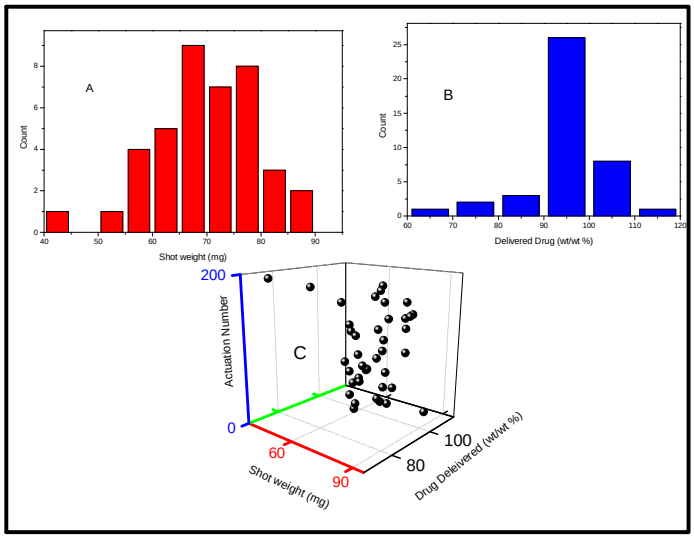


Fig. 4. 3D plot of concentration of the delivered drug versus actuation weight in relation to the actuation number

clusters are randomly spread. Further actuations result in a continuous growth of the drug islands inter-connected to- form semi-continuous or continuous aggregate layers.

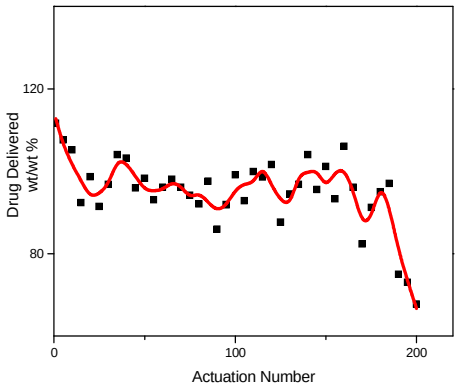
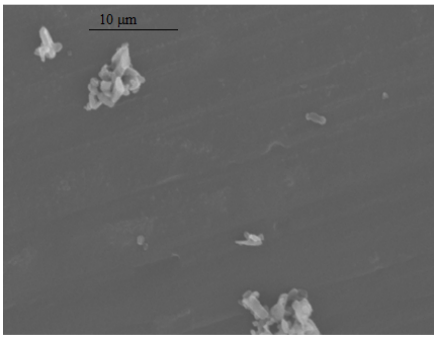
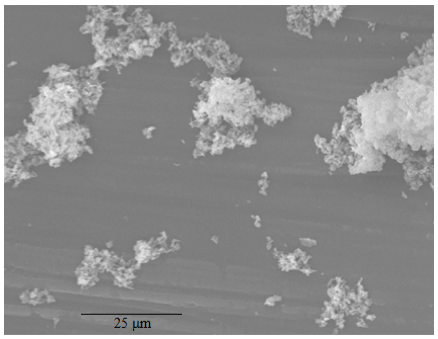


Fig. 5. Plot of the samples concentrations (wt/wt %) of the delivered drug versus the number of actuation increases

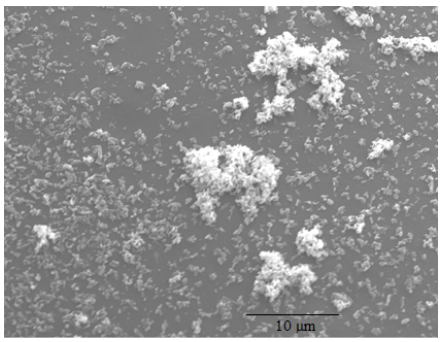
The Salbutamol Sulphate particle islands grown onto the internal surface of the chamber is graphically shown in Fig. 6. The figure shows that the growth of particles starts at an early stage of using the MDI device. After 15 actuations, particles of Salbutamol Sulphate were found to attach to the surface of the chamber, drug crystals deposited on the polymer surface as single crystal or small aggregated. Fig. 6A (after 15 actuations) shows the drug particles which spread over the surface without any preference to a particular order. With the increasing number of actuations 50 actuations, the growth of clusters and aggregations increases too. The inside surface area of metering chamber shows a buildup of islands/ clusters (Fig. 6B). In Fig. 6C, after 150 actuations, it shows that a large area was covered by layers of drug particles. As the actuation numbers increased (up to 100 actuations) the deposition of drug particles significantly increased in the chamber, forming a dense carpet of drug particles covering most of it.



A (WD 13 mm 20.0 KV. X 500. 10 µm)



B (WD 13 mm 20.0 KV. X 500. 10 µm)



C(WD 13 mm 20.0 KV. X 500. 100 µm)

Fig. 6. SEM image of a internal surface of the contant volume metered chamber, which had been exposed to different number of actuations. (a) 15 actuation. (b) 50 actuations. (c) More than 150 actuations

So the consecutive usage of the MDI device deposit a significant amount of Salbutamol Sulphate particles deposited on the surface of the inner part of chamber of MDI device, particles attached as single crystals and layers of drug particles.

Deposited molecules of Salbutamol Sulphate molecules were isolated for further investigation. The IR spectra of the standard samples and those of the deposited molecules collected from the internal surface of the constant volume of metered chamber revealed that no new bands disappear or arise on the vibrational spectra, as a result of the interaction between drug molecules and the internal surface which indicates that this interaction is physisorption.

4. CONCLUSION

Results obtained from the stimulated use test shows that none of the tested MDI devices has consistency in their shot weights. The shot weight was found to oscillate around 67.5 mg per actuation which could be attributed to sample conditions (i.e. possible temperature leakage and storage conditions). Moreover the concentration of delivered Salbutamol Sulphate was found to decrease with the extended use of the inhaler. The observed loss of Salbutamol Sulphate concentration is attributed to the deposition of Subutamole molecules onto the internal surface of the metering chamber of the MDI device. Both SEM images and spectroscopic analysis of the deposited particle onto the internal surface of metered chamber reveals that: (i) Micronized particle Salbutamol Sulphates accumulates onto that surface after a few actuations and starts to build up as actuations increase. (ii) These particles were attached onto the internal surface as single crystals and layers. (iii) The interaction between drug molecules and the internal surface of MDI is classified as physisorption since no vibrational bands arising or disappears as a result of the drug-polymer interaction.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Aaltoa A, Härkäpää K, Aro A, Rissanen P. Ways of coping with asthma in everyday life validation of the asthma specific coping scale. J Psychosom Res. 2002;53:1061–1069.
2. Ayres J, Jyothish D, Ninan T. Brittle asthma. Paediatr Respir Rev. 2004;5:40–44.
3. Bond R, Spina D, Parra S, Page C. Getting to the heart of asthma: Can “β blockers” be useful to treat asthma? Pharmacol. Ther. 2007;115:360–374.
4. Terzano C. Pressurized metered dose inhalers and add-on devices. Pulm Pharmacol Ther. 2001;14:351–366.
5. Gustavo J, Rodrigo, Luis J, Nannini. Comparison between nebulized adrenaline and b2 agonists for the treatment of acute asthma. A meta-analysis of randomized trials. Am J Emerg Med. 2006;24:217–222.
6. Michael Y, Snowden MJ, Chowdhry BZ, Ashurst IC, Davies-Cutting CJ, Ripley T. Characterisation of the aggregation behaviour in a salmeterol and fluticasone propionate inhalation aerosol system. Int. J. Pharma. 2001;221:165–174.
7. Young P, Price R, Lewis D, Edge S, Traini D. Under pressure predicting pressurized metered dose inhaler interactions using the atomic force microscope. J. Colloid and Interface Sci. 2003;262:298–302.
8. Traini D, Young P, Rogueda P, Price R. The use of AFM and surface energy measurements to investigate drug-canister material interactions in a model pressurized metered dose inhaler formulation. AEROSOL SCI TECH. 2006;40(4):227-236.
   DOI: 10.1080/02786820500543316
9. Peyron ID, Brittoco IL, Benissan LB, Tardieu BZ. Development and performance of a new hydrofluoroalkane (HFA 134a)-based Metered Dose Inhaler (MDI) of salmeterol. Respir Med. 2005;99: 20-30.
10. Angela C, Anderson MD, FAAP. Management of beta-adrenergic blocker poisoning. Elsevier; 2008.
11. Bièvre P, Gűnzler H. Validation in chemical measurement. 1st edition, Springer; 1999.
12. Diamant Z, Boot D, Kamerling I, Bjermer L. Methods used in clinical development of novel anti-asthma therapies. Respir Med. 2008;102:332–338.
13. Halabi A, Ferrayoli C, Palacio M, Dabbene V, Palacios S. Validation of achiral HPLC assay for (R)-salbutamol sulfate. J Pharm Biomed Anal. 2004;34:45–51.

14. Ouyang J, Li Duanc J, Baeyens W, Delanghe J. A simple method for the study of salbutamol pharmacokinetics by ion chromatography with direct conductivity detection. Talanta. 2005;65:1–6.

15. Zhang J, Xu Y, Di X, Wu M. Quantitation of salbutamol in human urine by liquid chromatography– Electrospray ionization mass spectrometry. J. Chromatogr. B. 2006;831:328–332.

Peer-review history:
The peer review history for this paper can be accessed here:
http://sciencedomain.org/review-history/13284