

**PRODUCT QUALITY AND CUSTOMER PERCEPTION OF PRESSURIZED METERED DOSE INHALER (pMDI) MANUFACTURED IN BANGLADESH**Abdur Rashid^{1*}, An-Nurul Masud², Nazrul Islam³ and Ayman Allahham¹¹ Department of Pharmaceutics, Buraidah College of Pharmacy and Dentistry, Al-Qassim, Kingdom of Saudi Arabia² GlaxoSmithKline Bangladesh Limited, Gulshan-1, Dhaka-1212, Bangladesh³ Pharmacy Discipline, School of Life Sciences, Queensland University of Technology, Brisbane Queensland - 4001, Australia*Corresponding author e-mail: rashid.uq@gmail.com**ABSTRACT**

This study was aimed to investigate the *in-vitro* deposition, the market status and the customer's perception of different pressurized metered dose inhaler (pMDI) preparations, available in Bangladesh. In order to test the efficiency of pMDI, the *in-vitro* deposition of locally manufactured salmeterol xinafoate from two brands, considered as product A and product B, was carried out using a Twin-Stage-Impinger (TSI) and was correlated with the customer perception. The market status and customer's perception has been studied through three different market surveys conducted on patients, (n=50), physicians (n=50) and pharmacy shops (n=50). In all three surveys the usage pattern of salbutamol has been found to be highest among various antiasthmatic drugs and has showed market share of 18.2 %. The manufacturer of this product occupied the highest market share compared with those of others. The *in-vitro* deposition of salmeterol xinafoate from both products revealed that the fine particle fractions (FPF, the amount of deposited salmeterol xinafoate in the lower airway of lung) of these products were within 32-44% and deposition was observed to be higher for product A compared to product B. Both the market status and efficiency testing results indicated that product A showed superior performance and more efficacy compared to the product B.

Key words: Asthma, Pressurised Metered Dose Inhaler, Fine Particle Fraction, In-vitro, Salmeterol Xinafoate and Salbutamol Sulphate.

INTRODUCTION

Asthma is a chronic inflammatory disorder of lung characterized by hyperactive airways, leading to reversible bronchoconstriction (Ramzi *et al.*, 2002). An obstructive condition of respiratory tract in which widespread narrowing of the bronchial airways occurred due to asthma (Walter and Israel, 1996). Dust, certain food, medicines, mites, mold spores and pollen are considered to be the main causes of asthma, which attack all age groups. It is a disease characterised by recurrent attacks of breathlessness and wheezing. Asthma is a chronic health hazard in Bangladesh where the prevalence of asthma is quite

high and a recent study reports showed that about 7 million people (5.2% of total population) are suffering from mild to moderate asthma while the fundamental cause of the asthma is still unknown. Almost four million children or 7.4 per cent of the child population of the country suffer from asthma and majority of such patients has mild asthma (Hassan *et al.*, 2002).

Various types of medications in various dosage forms including solid tablet, liquid for oral delivery and inhalers for direct delivery of drugs through the respiratory airways, are used to manage mild to moderate bronchoconstriction. Of the inhalers, i.e.

pressurized metered dose inhalers (pMDI) and dry powder inhalers (DPI), pMDI are frequently used in Bangladesh. The drug formulation in pMDI is usually a suspension or solution of drug in a liquefied propellant. Although pMDI are widely used in respiratory drug delivery, some problems have been associated with these devices, including the need for coordination of inspiratory inhalation with valve actuation and the use of a propellant which has possible adverse effects on the stratospheric ozone layer. Presently, there are some pMDI products approved by regulatory agencies with non-CFC propellants, i.e. hydrofluoroalkanes (HFA). However, the compatibility of the valves and container walls of some devices with HFA is also known to be problematic (Crowder *et al.*, 2001). In addition, the drug deposition from these inhalers is not more than 20-30% (Steckel and Mueller, 1997). Dry powder inhaler (DPI) contains the drug in a powder formulation. Powder de-agglomeration and aerosolization from these formulations are achieved by the patient's inspiratory airflow. This airflow needs to be sufficient to create an aerosol containing respirable particles, i.e. $<5 \mu\text{m}$ for lung deposition (Hersey, 1975). Advantages of DPI over other inhaler systems are the independence of breathing coordination with dose actuation, the absence of propellants, low innate initial velocity of particles (reducing inertial impaction at the back of the throat) and the solid state drug stability. However, here in this paper only the pMDIs has been studied, because no preparation of DPI are manufactured locally at the time of the study.

For proper management of mild to chronic asthma, the current available hospitals in Bangladesh have no such modern facilities. Although some hospitals have special arrangement to supply inhalers; however, this supply is inadequate with the increasing number of asthma patients. The poor patients can't afford relatively expensive inhalers. The marketing strategies of different expensive pressurized metered dose inhalers may affect the consumption of these drugs by the patients as around 70% people, who suffer from asthma, are from low socio-economic class and can't afford the cost effective inhalers.

Therefore, the objective of this study was to investigate the *in-vitro* deposition, the market status and the customer's perception of different pressurized metered dose inhaler (pMDI) preparations, available in Bangladesh. A survey was conducted to the patients, physicians and pharmacy shops to determine how antiasthmatic drugs are being used by the patients and the proportion of total sales of antiasthmatic drugs manufactured and/ or available in

Bangladesh. In addition, the efficiency of two brands of Salmeterol Xinafoate and salbutamol sulphate pressurized metered dose inhalers, manufactured in Bangladesh were carried out using TSI, an instrument to quantify the amount of drugs deposited in the lower airway of lungs during respiratory delivery, to compare with the efficiency and marketing strategies of these products.

MATERIALS AND METHODS

A: Survey work and marketing strategies: This study did not conduct the survey for finding the prevalence of asthma disease in the surveyed area; however, the survey conducted to find out how the patients are suffering from asthma, how they are managed and their impact on the marketing strategies of the leading pharmaceuticals, who manufacture the inhalers. Using surveys, work primary data were collected from patient, doctor and pharmacy owner by interviewing them through a questionnaire. The information was collected by face to face interviews and discussions with each individual of patient, physician and chemist. Primary data were also collected through observation. The secondary data are collected through the journal, medicine report, articles etc. The information of inhaler profile of Bangladesh was collected from the secondary data. The sampling procedure is non-probability sampling because the sample size is specific number and the method of sampling is judgmental.

Data Analysis: Collected data was organized and analysed by statistical methods and were interpreted by the relative weights and their significance.

B: Drug dispersion test

Collection of Sample: Three samples from each of products A and B (a preparation of Salmeterol Xinafoate) inhalers were collected from the retail pharmacy of different areas in Dhaka city (Bangladesh). The manufacturing date was close to each other to avoid difference in expiry date. Collected samples were covered with security seal by manufactures.

Drug dispersion by Twin-Stage Impinger (TSI):

The *in-vitro* aerosol deposition of Aerosol formulations has been determined using a Twin-Stage Impinger (TSI, Apparatus, A; British Pharmacopoea, 2000) (Copley, UK).

The actuator adapter was placed in position at the end of the throat so that the mouthpiece end of the actuator, when inserted to a depth of about 10 mm, lines up along the horizontal axis of the throat while

the open end of the actuator, which accepts the pressurized container, was uppermost and in the same vertical plane as the rest of the apparatus.

A solvent of 50 % (v/v) methanol (HPLC grade) was used as the collection liquid with 7 and 30 ml were placed into stage one and stage two of the TSI respectively. The temperature and relative humidity of the surrounding environment was measured by a thermo-hygrometer (Shinyei TRH-CZ, Japan). A suitable vacuum pump (Model OD5/2, Dynavac Engineering, Australia) was connected to the outlet of the apparatus and the airflow rate was adjusted to 60L/min at the mouthpiece (Fisher and Porter, Model 10A3567SAX, UK).

The metering valve was primed by shaking for 5 seconds and discharged once to waste and this process was repeated for further four times. The container was again shaken for 5 seconds and assembled the mouthpiece end of the actuator in the adapter, the pump was switched on and drug was discharged once immediately. The assembled inhaler was removed from the adapter, shaken for not less than 5 seconds and relocated the mouthpiece end of the actuator for a further eight times. After discharging the tenth delivery, the pump was switched off after 5 seconds. The apparatus was then dismantled and the inner surface of the inlet tube to the lower impingement chamber and its outer surface that projected into the chamber (stage 2) were washed with 50% (v/v) methanol solution. This solution was combined with the collecting solvent previously kept in stage 2 of the apparatus. The amount of Salmeterol Xinafoate in this solution was determined by HPLC and was expressed as the fine particle fraction (FPF), which is defined as the amount of drug particles deposited in the lower stage (stage 1) of the TSI. The

deposition of drugs from the pMDIs is very complex and depends upon so many factors, including complex physiology of respiratory tracts (Vander *et al.*, 1994), co-ordination between drug actuation and patient's inspiration, physicochemical properties of drugs and propellants, inspiratory flow rate and resistance of device (Hickey and Martonen, 1993; Martonen and Katz, 1993; Steckel and Mueller, 1997). Therefore, it is very difficult to predict the amount of drugs to the lower airway of lungs from the inhalers.

HPLC analysis of Salmeterol Xinafoate: Salmeterol Xinafoate was analyzed by High Performance Liquid Chromatography (HPLC) using a C₁₈ column (μBondapak™, 3.9 x 300mm, Waters) and an UV detector (Waters Tunable Absorbance Detector, USA) at a wavelength of 252 nm. A mixture of methanol and 0.2% (w/v) ammonium acetate solution (55:45, pH ~6.9) was used as a mobile phase running at a flow rate of 1.0 ml/minute by a HPLC pump (Waters 510, USA). The peak area was recorded by integration (Shimadzu CR6A Chromatopack, Japan). The retention time of Salmeterol Xinafoate was 3.89 minutes. The calibration plot of standard Salmeterol Xinafoate solution was linear over the range of 0.4-10 μg/ml with r²=1.00.

Calculation: The recovered dose (RD) was defined as the total amount of drug collected from stage one (S1) and stage two (S2). The emitted dose (ED) was defined as the amount of drug delivered from the inhaler presented as the percentage of RD. The fine particle fraction (FPF) was defined as the amount of drug particles deposited in the lower stage of the TSI as a percentage of the ED. Both ED and FPF were calculated using the following equations:

$$ED = \frac{S_1 + S_2}{RD} \times 100 \quad (1)$$

$$FPF = \frac{S_2}{ED} \times 100 \quad (2)$$

RESULTS AND DISCUSSIONS

A: Survey work

Survey of asthma patients: The outcome of the survey revealed that most of the respondents (68%) have been suffering from asthma for more than three years; 12% for three years, 10% for two years and 4% for one year (Rashid *et al.*, 2008). With regards to the epidemiology of asthma in the surveyed area, the outcome might not represent the severity of this disease of the whole country because of the limited

numbers of patients that have been surveyed within three regions of the greater Dhaka city; however, this result would help to get an idea of the severity and management of asthma in these areas. Dhaka is a big city with very dense population and with environmental pollution by dust, gas, and smokes from malfunctioning vehicles, which cause to increase the severity of asthma disease. That's why the number of asthma patients is increasing day by day in the greater Dhaka city.

Management of Asthma

Prescription pattern by physicians: The prescription pattern by the physicians revealed that the physicians prescribe inhalers frequently. The survey indicated that 38% physicians prescribed about 80% of inhaler in total drugs prescribed per day and around 28% physicians prescribed 50% inhalers of the total prescription per day. Surprisingly, the survey indicated that 8% and 4% physicians prescribed 100% and 90% inhalers respectively, per day. This pattern of prescription disclosed the severity of asthma patients in the surveyed area. During prescribing, 64% of physicians considered the financial condition of the patients whereas 6% physicians did not consider the financial condition of consumers, and 30% physicians discarded this question. Most physicians preferred according to the rank order of the combination of salmeterol xinafoate (SX), salbutamol sulphate (SS), Fluticasone propionate, and beclomethasone dipropionate (BD) (Table 1). Few physicians were found to prescribe

other drugs such as Nedocromil, Na-chromoglycate and Triamcinolone acetate. It is interesting to note that the visiting frequency of medical representatives to physicians did not influence the market share of those products.

Survey showed that physicians preferred different manufacturers considering the efficacy, quality, availability, cost of products, company image and motivated by personal relationship with medical representatives of the respective manufacturers. Considering the previous parameters, a multinational company appeared to be the high ranked pharmaceutical company compared with those of local industries. The effectiveness and good quality of products, although not quantitative, was concluded by physicians according to their interpretation of the patient response during treatment. However, company image and marketing strategies of manufacturers also strengthen these two parameters.

Table 1: Preferred drugs by Physicians.

Generic name of different products	Weighted score	Market share (%)
Beclomethasone diproponate	272	5.7
Fluticasone propionate and Salmeterol xinafoate	272	2.2
Salbutamol sulphate	298	18.2
Salmeterol xinafoate	350	6.6
Nedocromil sodium	213	1.2
Sodium chromoglycate	121	2.0
Triancenolone acetoneide	184	2.4

Usage pattern of drugs by patients: To manage asthma, steroids, salbutamol sulphate and salmeterol xinafoate pressurized metered dose inhalers (pMDIs) were used by 63.6%, 25% and 9.1% patients, respectively, either prescribed by the physicians or recommended by other patients who are using the same medicine, or influenced by the pharmacy shops. Out of the steroid drugs, Beclomethasone diproponate was found to be used frequently, compared with those of salbutamol sulphate and salmeterol xinafoate. After consulting with doctors, about 50% patients changed their medicines due to the less efficiency of inhalers. Although unacceptable, study revealed that around 10% patients changed their inhalers by themselves or by consulting with their friends who used that medicine; however, only 2% patients changed due to high price of some inhalers. This result revealed that drugs are not sold or used

according the recommendation of physicians. It is amazing to note that about 46% of the patients motivated other patients to take specific brands of the inhaler without consulting with doctors. For example, around 22% of patients suggested taking salbutamol sulphate, whereas 12% recommended salmeterol xinafoate. It was unclear how one patient motivated other patients to buy specific brand, however, it could be due to better relief of asthma experienced by the motivator.

Although inhalers are being prescribed by doctors either specialist or GP, uses of higher percentage of steroids inhaler could be a long term problem where a significant number of patients have a greater tendency to change their medication without consulting with their doctors. It indicated that the patients did not follow the physicians or mislead by pharmacy shops.

In this case, patients need to be familiar with the proper instruction to use medicaments through inhalers and the doctors need to inform all possible health hazards to the patients.

The consumers were found to be aware of the quality of drugs before buying. The preference of buying medicines indicated a rank decrease in the quality, effectiveness, and company image (Figure 1).

According to the effectiveness, the most preferred drug was Beclomethasone dipropionate compared with those of salbutamol sulphate and salmeterol xinafoate. Of the manufacturers, according to the patients view, a multinational industry was found to be the highest quality manufacturer of pMDIs and occupied the highest percentage of usage. A leading local manufacturer was ranked in the second position, however very close to that multinational company.

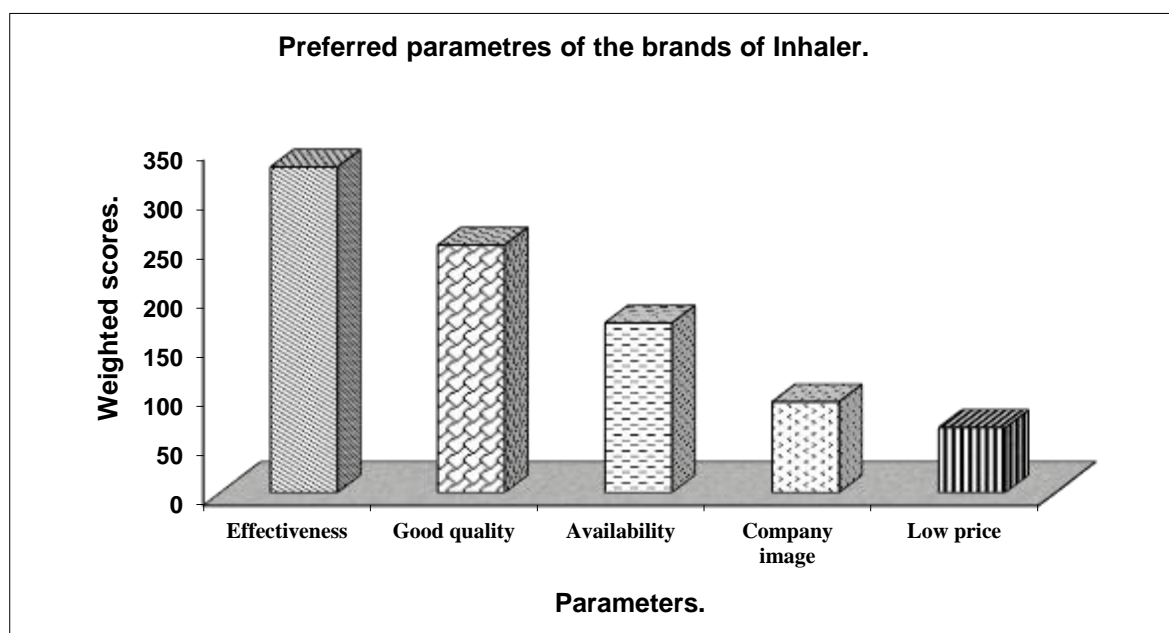


Figure 1. Preferred parameters regarding the brands of Inhaler.

Selling pattern by the pharmacy shops: From the survey work, about 76% (38 of 50) respondents revealed that they sold most of the inhaler according to prescription and 24% (12 of 50) did not follow the physician's prescription. A major portion (74%) of sellers was found to influence the patients for buying medicines according to the prescription whereas 26% sellers influenced the patients to buy without prescription. It is surprising to note that a significant number of respondents (42%) said that more than 10% of inhalers are sold as over the counter drug

(OTC). The survey also indicated that most of the respondents have given priority on patient's demand, effectiveness of drugs, and profit of the business (Table 2). Other remarkable parameters were prescription by physicians, product quality, availability of products, and good relationship with medical representatives (MR). The majority of the respondents (32%) commented that the inhaler price should be reasonable, 26% replied both quality and price and only 16% replied quality should be high.

Table 2: Preferred parameters of pMDIs.

Rank	Parameters	Weighted score
1	Patients demand	416
2	Profit	225
3	Physicians prescription	163
4	Quality of products	159
5	Availability of products	67
6	Relationship with MR	32

Market share of different products: The market share of different pMDIs manufactured by different pharmaceutical companies was summarized in table 1. Salbutamol sulphate captured the highest market share (18.2%) of the total inhalers and the next products were salmeterol xinafoate and steroids containing preparations. With regards to the market share of the four pharmaceutical companies who manufacture metered dose inhalers in Bangladesh, the multinational company captured the highest market share (48.7%, the raw data not shown in this article) and the second highest position occupied by a leading local manufacturer (38.0%, the raw data not shown in this article). These findings coincided with the company image in the perception of physicians, patients and pharmacy shops, who represented the products of those companies in the rank order of quality and efficacy. As discussed earlier, the market share of salbutamol sulphate, salmeterol xinafoate and beclomethasone dipropionate were found to be higher than those of other products and was consistent with the usage pattern of these drug by the

patients either prescribed by the physicians or not. For the steroid preparations, a diffused pattern of preference revealed that physicians mostly preferred a brand whereas patients preferred another brand, meaning that those drugs were not sold according the prescription. Market share of inhaler in pharmacy varied according to the sales position of the brand, image and reputation of company. In this study, the market share was seen according to the four major competitive inhaler manufacturing company. It is clear that there are few brands among those competitors that indicate the super competition to capture the market by advertising where the law enforcement in controlling the advertisement were insufficient resulting in increasing their brand loyalty with physicians, patients and pharmacy shops.

Part B: In-vitro drug deposition from selected pMDI: The in-vitro deposition of only Salmeterol Xinafoate contains products A and B was carried out and is shown in Table 3.

Table 3: Results of Salmeterol dispersion from products A and B (n= 3x2; 3 samples from each group and 2 replicates from each samples; standard deviations are within the brackets).

Salmeterol Xinafoate	Samples	ED	FPF (%)	Average FPF
Product A	1	100	49.3	44.2 (5.4)
	2	100	44.2	
	3	100	38.5	
Product B	1	100	44.3	32.3 (10.7)
	2	100	23.5	
	3	100	29.1	

The study showed that the Salmeterol xinafoate dispersion (FPF) from sample 1, 2 and 3 of product A was 49.3, 44.2 and 38.5%, respectively. In contrarily, the FPF from sample 1, 2 and 3 of product B was 44.3, 23.5 and 29.1 %, respectively. There is no specification in any standard official books about the percent deposition of drugs from the inhalers during respiratory delivery, except that the dose content uniformity should be 80-120 percent. Emitted dose (ED) of salmeterol xinafoate from each device was 100%; however, *in-vitro* deposition i.e., FPF of product A (FPF 44.2 ± 5.4 %) was found significantly ($p < 0.05$) larger than that of product B (FPF 32.3 ± 10.8 %). The dose variability of product B (standard deviation, 10.8) was higher than that of product A (5.4). The reason behind this was unknown; however, the device resistance could be a factor in influencing FPF and dose variability. The first sample of product A produced good deposition, FPF 45-54%, 2nd sample, FPF 44-46%, and 3rd sample FPF 36-40%.

Similarly product B produced very good FPF for first sample (FPF: 37-50%), whereas for 2nd (FPF, 21-26%) and 3rd sample FPF 28-29%, very poor performance (Rashid et al., 2008). These results indicated that batch-to-batch variation in FPF was significantly ($p < 0.05$) higher for product B compared with product A. Dispersion from product B has been also found less reproducible than that of product A. Further investigation in terms of determining device resistance and its influence in controlling dose delivery is warranted.

Combination of survey and in-vitro dispersion of some selected brands: The overall marketing strategies, physicians and patient's feedback on the quality and efficacy of only two brands (product A and product B) were compared with the *in-vitro* respiratory delivery of drugs from these two brands and the results were presented in Table 4.

Table 4: Different quality and marketing parameters of two brands of Salmeterol Xinafoate.

Selected Parameters								
Product	Drug deposition	Market share		Used by patients	Preferences			Visit of MR
		Product	Manufacturer		Physicians	Patients	Chemists	
A	(44.2%)	(18.2%)	(48.7%)	(25.0%)	High	High	High	Low
B	(32.3%)	(6.6%)	(38.0%)	(9.1%)	Low	Low	Low	High

The comparison gave an insight look on different quality and marketing parameters of the two brands of Salmeterol Xinafoate manufactured in Bangladesh. The in vitro deposition data showed that product A had superiority over B. Product A has also been found superior while considering different marketing parameters of this drug as well as previously described market share. However, visiting of doctors by medical representative (MR) was higher for product B than that of product A. Taking into account the results in Table 4, it may be concluded that product A was found to be superior to B considering all parameters used in this study. This combination of efficacy and quality leads to get more preference by the physicians, chemists and patients resulted in increasing market share of product A.

Conclusions

The marketing status of different pMDIs and their manufacturers suggested that the quality and efficacy of drugs were given priority by physicians, patients and sellers. However, there was a greater tendency among the patients and sellers to avoid prescription during buying or selling those inhalers. It was also found that incidences of over the counter (OTC) sale of inhalers and motivation by patients are practiced. These trends should be discouraged by providing adequate information to patients and chemists above the possible hazards of pMDI on our health. The combination of efficacy and drug delivery i.e. drug deposition of the two brands would lead to get preference by the physicians, chemists and patients and thereby affect the market share.

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