International Journal of Engineering Research & Management Technology
ISSN: 2348-4039
December-2018 Volume 5, Issue-6
Email: editor@ijermt.org www.ijermt.org

PERFORMANCE EVALUATION OF DIFFERENT BRANDS OF SALBUTAMOL SULPHATE SYRUP

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ABSTRACT
Salbutamol Sulphate is a short-acting β2-adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease (COPD).It is widely produced and marketed drug by many pharmaceutical companies in Bangladesh. Five different brands of Salbutamol Sulphate syrup manufactured by Bangladeshi pharmaceutical companies were collected from different retail pharmacy of Noakhali and Dhaka, Bangladesh. The performance evaluation (Appearance, Organoleptic properties, Potency, Density, Microbial Assay, Viscosity, pH) was carried out in order to find out whether they really complied the required standards. As a part of evaluation of organoleptic properties color, flavor, taste, container type, specially clarity of representative samples of each pharmaceutical companies were evaluated and they were clear with acceptable color, flavor and taste. The results of viscosities, density, and pH of all of them were satisfactory. The potency of the representative samples was determined and out of five samples, result of four samples was satisfactory. This study was conducted to determine the microbiological quality of syrups of different brands. Microbiological analysis was carried out using spread plate technique on culture media. Hence potential safety measurement should be taken during the production and use of asthma syrups to maintain the microbiological quality.

KEYWORDS: Salbutamol Sulphate, Potency, Density, Microbial Assay, asthma, Bangladesh

INTRODUCTION
The assessment of drug product performance is important since bioavailability is related to the pharmacodynamics response and related adverse events. Thus, performance tests relate the quality of a drug product to clinical safety and efficacy.[1] Performance evaluation is the part of identifying the quality and effectiveness of a product. As drug products are the life saving product so strength, quality, purity, and identity including also the packaging, storage, and other requirements and specification should be good for us. The term "quality" has a relative meaning. This is expressed by the ISO definition: "The totality of features and characteristics of a product or service that bear on its ability to satisfy stated or implied needs".[2]Every pharmaceuticals industry tried to maintain good quality to keep up its reputation and capture the competitive market demand. The total number of brands /items of salbutamol sulphate that are registered in Bangladesh is currently estimated to be 97, while the total number of salbutamol sulphate syrup is 37.[3] Salbutamol, also known as albuterol and marketed as different brand name and use as a medication that opens up the medium and large airways in the lungs.[4] Salbutamol sulphate syrup generally used for the treatment of asthma, exercise-induced bronchospasm, and chronic obstructive pulmonary disease (COPD).[5] Salbutamol Sulphate syrup is mostly taken by the inhaled route for direct effect on bronchial smooth muscle. This is usually achieved through a metered-dose inhaler (MDI), nebulizer, or other proprietary delivery devices. The most common side effect of Salbutamol is fine tremor of the hands, which may interfere with precise manual work. Tension, restlessness and a rapid heartbeat may also occur[6] by performance evaluation marketed drug's efficacy can be determined. Different side effects that occur due to potential problems of drugs can be identified among the marketed drug. This can be helpful for the patient to select the best one. Apart from the serious side-effect which is inherent in the drug itself, such as teratogenicity, a medicinal product can become unsafe due to many other factors such as cross-contamination, contamination with pathogenic organisms, very high or low potency, wrong labeling, inadequate packaging and storage

conditions. So a careful and rational evaluation should be needed.[7] the major purpose of this project work is to find out the current status of the quality of the marketed Salbutamol Sulphate syrup preparations available in Bangladesh. This project work makes awareness among the people's health, health practitioners and drug control authority so that pharmaceutical manufacturers produce quality medicine and people may not waste their hard earning money by buying low quality product.

MATERIALS AND METHODS

Collection of Sample: Samples from top, middle and lower category pharmaceutical companies were randomly selected. Samples were collected from retail medicine shop of different areas of Bangladesh. Diagrammatically the size and nature of the areas from where the samples were purchased are shown in figure 2. The samples were properly checked for their physical appearance, name of the manufacturer, batch number, manufacturing data, expiry date, manufacturing license number, D.A.R. number and maximum retail price at the time of purchase.

Status of the Samples: Salbutamol Sulphate syrups were sugar and agglomerate-free and homogenous. Five different available brands of syrups of various manufacturers were purchased for the analytical studies.

Reference: The BP reference standard of Salbutamol Sulphate was obtained from GlaxoSmithKline Pharmaceuticals Ltd as gift sample for research work. The purity of the reference standard was 100.90%.[8]

Coding of Syrup: Five Salbutamol Sulphate syrup brands collected from five different pharmaceutical companies were coded as

- SAL 01
- SAL 02
- SAL 03
- SAL 04
- SAL 05

Apparatus Used in This Study:

Table 1: Name of glassware

Name of the glass ware	Manufacturer / Source
Measuring cylinder (50 ml)	India.
Beaker (50 ml ,100 ml)	Gilin Brand, China.
Pipette (1 ml ,2 ml ,5 ml ,10 ml)	Precicolor (HBG), Germany.
Funnel (75 mm)	Wheel Brand, China.
Filter paper	India.

Table 2: Name of the Instrument

Name of the instrument	Manufacturer
Analytical balance	Ohaus CP213, China
Oswald Viscometer	China.
UV-Spectrophotometer	PG instrumentation, England
pH meter	Switzerland.
Picnometer	China
Conical flask	China
Petri dies	Switzerland
Laminar air flow	Japan

PHYSICAL ANALYSIS

Organoleptic test of syrup: The analysis of the properties of products and materials by means of the sense organs

Procedure: Suitable amount of Salbutamol Sulphate syrup was poured in a beaker. Visual observation was evaluated for appearance of syrup such as color, homogeneity, transparency, taste and the flavor by allowing syrup to expose to normal conditions without any packaging stored at room temperature.

Density determination of syrup: The analysis of the density of the syrup was done by using picnometer. Density was measured by the following equation-

$$\rho = w/V$$

Where, ρ is the density, *w* is the weight of sample and *V* is the volume.

Viscosity determination of syrup: The viscosity of the syrup was done by using Ostwald viscometer. Same volume of liquid was introduced in second bulb and time of flow of liquid was measured as before.3 readings and mean of them was taken.
Then viscosity of a given liquid was calculated by using the following formula-

$$\eta_1 \rho_2 t_2 = \eta_2 \rho_1 t_1$$

Where, η_1 and η_2 are viscosity coefficients of the liquid and water, and ρ_1 and ρ_2 are the densities of liquid and water, respectively.

pH measurement of syrup:
Suitable amount of syrup was poured in a beaker. pH meter was immersed into the syrup.
Then pH value was noted at room temperature.

CHEMICAL ANALYSIS

Preparation of standard curve: To prepare a standard solution, 20mg of Salbutamol Sulphate was weigh by the electronic balance and placed in 100ml volumetric flask. Then a series of standard solution of standard Salbutamol Sulphate e.g. 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml, 16µg/ml, 18µg/ml, 20µg/ml etc. were prepared by proper dilution by using 0.1N HCl. Then absorbance were taken at 278 nm against blank for each solution and the average was calculated which has been given in Table-3.

Table 3: Absorbance of different concentration of standard Salbutamol sulphate solution measured at 278 nm

Concentration (µ g/ml)	Absorbance	Average of the absorbance
2	0.029 0.030 0.028	0.029
4	0.039 0.038 0.040	0.039
6	0.151 0.150 0.152	0.151
8	0.173 0.172 0.174	0.173

10	0.188 0.187 0.189	0.188
12	0.242 0.241 0.243	0.242
14	0.125 0.124 0.126	0.125
16	0.140 0.139 0.141	0.140
18	0.205 0.204 0.206	0.205
20	0.168 0.167 0.169	0.168

Preparation of standard solution: To prepare a standard solution, 20mg of Salbutamol Sulphate was weigh by the electronic balance and placed in 100ml volumetric flask. Then the concentration of solution was attained 100µ g/ml by adding 0.1N HCl by proper dilution with 0.1N HCl.

MICROBIAL ASSAY OF SYRUP

Preparation of Agar plates: Nutrient agar is a general purpose medium supporting growth of a wide range of non-fastidious organisms. 100 ml agar media was prepared and sterilize the media in an autoclave at 120º C, 15 psi for 20 min. Prepared the working area was suitable for the Laminar air flow area. The plates were labeled with the type of media and poured into them. Swirled the hot media vigorously to mix. The media was cooled until it was just cool enough to handle, about 20–30 minutes. Swirled the media again to mix just before pouring; be careful not to incorporate bubbles. Poured into plate until it covers the bottom, approximately 25ml. Plates will keep refrigerated for few minute.

Sample Collection: Five different brands of Salbutamol Sulphate syrups were purchased from the local pharmacy stores of Noakhali and Dhaka, Bangladesh on December 2015.

Enumeration technique: The microorganism was enumerated by methods described by the Fawole and Oso and compared by with the standard of microbiological specifications for certification of syrups.[9]Using the spread plate technique, each sample of the syrup was vigorously shaken; 0.1 ml was withdrawn and diluted serially (10 fold dilution) in sterile normal saline. A quantity of 0.1 ml of the diluted sample was spread on the surface of Tryptone Soy agar and Sabouraud Dextrose agar (SDA) plates. Spread plate technique was used to enumerate the microbial contaminant from the collected syrup samples. One milliliter from each sample was withdrawn aseptically and transferred into 9ml normal saline for serial dilution to 10-3. Diluted samples were thoroughly mixed for the proper dissolution of the drug. 0.1ml of each sample was then inoculated into different culture media plates by spread plate technique. The suspensions were reconstituted with sterile distilled water and were thoroughly mixed and cultured as for the syrups. The Tryptone Soy agar plates were incubated at 37^{o}C for 24 hours while the SDA plates were incubated at 25^{o}C for 7 days with daily observation.[10] All experiments were done in duplicates and controls set up in each round. Colonies were counted and the mean number of colony forming units per ml of each syrup and suspension was calculated.

Isolation and Quantization: 0.1 ml of the each diluted sample was spread aseptically onto nutrient agar plate. Plates were then incubated for 24 hours at 37°C. Bacterial colonies were counted manually and average number of colony forming unit (cfu) was determined for each ml of the syrup sample.

Identification of Isolated Micro-organisms: The sample of the syrups was placed on various selective media such as Tryptone Soy agar and Sabouraud's Dextrose Agar (mould and yeasts). Growth characteristics, microscopy study and biochemical tests were used for the identification of isolates from the syrups. Samples were incubated for 24 hrs after which presence of growth was observed. The bacterial and fungal isolates were further identified using the standard media and biochemical analysis.

RESULTS AND DISCUSSION

Organoleptic evaluation of syrup: The organoleptic properties of five brands of Salbutamol Sulphate syrup were thoroughly analyzed according to the procedure and results are shown in the table 4

Table 4: Organoleptic evaluation of various brands of Salbutamol Sulphate syrup

Brand	Container	Color	Flavor	Taste	Clarity
SAL01	White glass	Yellow	Strawberry	Sweet	Clear
SAL02	Amber glass	Light green	Raspberry	Sweet	Clear
SAL03	White plastic	Orange pink	Vanilla	Sweet	Clear
SAL04	Amber glass	Colorless	Strawberry	Sweet	Clear
SAL05	White plastic	Light green	Raspberry	Sweet	Clear

Organoleptic properties of different brands of Salbutamol Sulphate syrup can be different. But color, flavor, taste of all brands should be acceptable & syrup of all brands must be homogenous.

PHYSICAL ANALYSIS

Table 5: Density of various brands of Salbutamol Sulphate Syrup

Sample code	Number of samples taken	Average density per sample (g/ml)	Number of samples within BP / USP range	Number of samples out of BP / USP range
SAL 01	5	0.996	5	0
SAL 02	5	1.181	5	0
SAL 03	5	1.007	5	0
SALO4	5	1.054	5	0
SAL 05	5	1.010	5	0

Specification of density of syrup: It is seen from the above results (Table 5) that none of the samples exceeded the specification for density. Therefore, it can be said that all the studied samples complied with the USP specification for density of syrup (≤1.380g/ml).[11]

Table 6: Viscosity of various brands of Salbutamol Sulphate Syrup

Sample code	Number of samples taken	Average viscosity per sample(cp)	Number of samples within BP / USP range	Number of samples out of BP / USP range
SAL 01	5	8.294	5	0
SAL 02	5	9.208	5	0
SAL 03	5	7.093	5	0
SAL O4	5	11.431	5	0
SAL05	5	10.038	5	0

BP Specification: for Salbutamol Sulphate syrup not all liquids are the same. Some are thin and flow easily, while others are thick and good and flow very slowly. A liquid's resistance to flowing is called its viscosity. The viscosity of a fluid is a measure of its resistance to gradual deformation by shear stress or tensile. For liquids, it corresponds to the informal notion of "thickness". For example, Syrup has a higher viscosity than water. In syrup, viscosity should be optimum. Because if it is more viscous then difficulties occur to withdrawal doses from the container and less viscous can increase the flow property of liquid. So it is difficult to measure the exact dose. It is seen from the above results (Table 6) that none of the samples exceeded the specification for viscosity. Therefore, it can be said that all the studied samples complied with the BP specification for density of syrup.

Table 7: pH of various brands of Salbutamol Sulphate syrup

Sample code	Number of samples taken	Average pH per sample	Number of samples within BP / USP range	Number of samples out of BP / USP range
SAL 01	5	4.35	5	0
SAL 02	5	4.12	5	0
SAL 03	5	4.02	5	0
SAL O4	5	3.76	5	0
SAL05	5	4.75	5	0

BP Specification: for Salbutamol Sulphate syrup.
It is seen from the above results (Table 7) that none of the samples exceeded the specification for pH. Therefore, it can be said that all the studied samples complied with the BP specification for density of syrup.

CHEMICAL ANALYSIS:

Table 8: Potency of various brands of Salbutamol Sulphate syrup

Sample code	Potency (mg/5ml)	Potency (%)	BP specification
SAL 01	2.0897	104.5	Specified
SAL 02	2.0573	102.8	Specified
SAL 03	1.9215	96.07	Specified
SAL 04	1.7086	85.43	Not Specified
SAL05	1.9850	98.01	Specified

Potency Determination of Salbutamol sulphate Syrup: The ingredients of syrup samples exert the therapeutic effect. The deficient potency will result in less therapeutic response or even the product may be

ineffective. From the above result (Table 8), it is observed that all brands of syrup meet the specification of potency 95-105% (BP-2012)[12]
From the above table it is shown that 3 brands meet the BP specification but one sample does not comply with specification.

Table 9: Summary of Microbial Count of Salbutamol Sulphate Syrup

Samples	Total Aerobic bacterial count (cfu/ml)	Total Fungal count (cfu/ml)	Acceptable limit of bacteria cfu/ml (USP)	Acceptable limit of fungi cfu/ml (USP)
SAL 01	7×10^2	1×10^2	$\leq 10^3$	$\leq 10^2$
SAL 02	6×10^2	8×10^1	$\leq 10^3$	$\leq 10^2$
SAL 03	8×10^2	3×10^1	$\leq 10^3$	$\leq 10^2$
SAL 04	5×10^2	7×10^1	$\leq 10^3$	$\leq 10^2$
SAL 05	7×10^2	4×10^1	$\leq 10^3$	$\leq 10^2$

Microbial Count of Salbutamol Sulphate Syrup: Acceptable limit of bacteria $\leq 10^3$cfu/ml and acceptable limit of fungi $\leq 10^2$cfu/ml for Salbutamol Sulphate syrup. (BP-2012)[13]
From the above result (Table 9), it is observed that all brands of syrup meet the specification of presence of microorganism. As such, of the five brands of commercially commonly used asthma syrups used in this study, no failed the test while five passed.

Table 10: Average Percentage Content of Salbutamol Sulphate Syrup in Different Samples

Drug codes	**Actual weight (g)**	**Percentage content (%)**	**Remark**
SAL 01	101.28	100.67	PASSED
SAL 02	98.53	97.43	PASSED
SAL 03	96.56	95.65	PASSED
SAL 04	97.43	96.54	PASSED
SAL 05	**98.50**	**97.35**	**PASSED**

CONCLUSION

Five brands' of Salbutamol Sulphate syrup was analyzed by using established method and calibrated apparatus in order to determine their quality. This study also helps to make comparison between different brands of Salbutamol Sulphate syrup manufactured by Bangladeshi pharmaceutical company. The present works reports comparative study of different brands of Salbutamol Sulphate syrup. It can be concluded that most of these syrup have passed the official requirement for microbiological quality, pH, and viscosity of syrups.it helps to the people to evaluate the quality full product from the market.

Moreover this study will help both physician and consumers to select quality product also this work can provide some information for Drug Control Authority of Bangladesh to evaluate the overall quality status of Salbutamol Sulphate Syrup. Salbutamol sulphate is a very important drug for the treatment of acute and chronic asthmatic attack. This study revealed that a good number of salbutamol sulphate preparations available in the pharmaceutical market of Bangladesh are substandard. Moreover, formulation error in

incorporation of sugars in Salbutamol sulphate liquid preparations was also detected by chemical assay study. Government regulatory authority should come forward and take necessary measures so that the manufacturers do not produce standard medicines and that formulation errors do not exist in pharmaceutical dosage forms.

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