# Study the Effect of Disintegrant Types on Preparation and *In-Vitro* Evaluation of Salbutamol Sulfate Effervescent Granules

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**Accepted: (November-2020) Published:( January -2021)**

## Abstract

**Background:** Many patients like elderly people, pediatric and persons with dysphagia find difficulty swallowing the tablets and thus do not comply with prescriptions.

**Objective** of this study was to prepare salbutamol sulfate and evaluate as effervescent granules in-vitro using superdisintegrant agent (Explotab) and traditional one (Avecil) for comparison study.

**Methods:** Three formulations (F1-F3) of effervescent Salbutamol Sulfate granules were formulated by the wet granulation method. Avecil, Explotab, Polyvinylpyrrolidone and other ingredients used in the formulation of effervescent granules. Evaluation tests were carried out for all three formulations include (particle size distribution, Flowability, effervescent time and percentage of drug release in 5 minutes).

**Results**: Formula that contain Avecil (F3) has better flow properties (angle of repose, carr's index and hausner's ratio) than other formula. The formula that contain Explotab (F2) has more effervescent time than others while the formula without disintegrant (F1) had more amount of drug dissolved than others.

**Conclusion**: Salbutamol sulfate was successfully prepared as effervescent granules to improve patient compliance.

**Keywords**: **Effervescent granules, Salbutamol sulfate, disintegrant agent, Avecil, Explotab.**

# دراسة تأثير انواع المواد المفككة على التحضير و التقييم خارج الجسم للسالبيوتامول بشكل حبيبات فوارة

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**الخلاصة**

**الهدف :** ان سهولة اخذ الدواء وامتثال المريض مهمة في صياغة أشكال الجرع الدوائية , العديد من المرضى مثل كبار السن والأطفال والشخص الذي يعاني من عسر البلع يجدون صعوبة في ابتلاع ألاقراص وبالتالي لا يمتثلون للوصفات الطبية. كان الهدف من هذه الدراسة هواعداد السالبوتامول سلفيت كحبيبات فوارة لتحسين امتثال المريض للدواء.

**الطريقة :** ثلاثة صيغ من حبيبات السالبيوتامول سلفيت الفوارة حضرت بطريقة التحبيب الرطب وذلك باستخدام الافسيل , الاكسبلوتاب , بولي فنيل بايروليدون وغيرها من المكونات وان دراسة التقييم التي اجريت لجميع الصيغ الثلاثة تتضمن (توزيع حجم الجسيمات و قابلية التدفق ووقت فوران الحبيبات والنسبة المئوية لانطلاق الدواء في خمسة دقائق) .

**النتائج :** الصيغة الثالثة التي تحتوي على الافيسيل لديها خصائص تدفق أفضل (carr's index ,angle of repose و hausner ratio ) من الصيغ الأخرى ، والصيغة الثانية التي تحتوي على الاكسبلوتاب لديها وقت فوران أكثر من غيرها في حين أن الصيغة الاولى التي لا تحتوي على مادة مفتتة كان لديها أكثر كمية دواء مذابة من غيرها.

**الاستنتاج:** تم تحضير سالبوتامول سلفيت بنجاح كحبيبات فوارة لتحسين امتثال المريض للدواء.

## Introduction

The oral dosage forms are the most popular method of drug administration, in spite of some disadvantages, like slow absorption, and thus the onset of action is time consuming. This can be overcome by administrating the drug in liquid form, but many active pharmaceutical ingredients have limited level of stability in liquid form [1]. Hence, effervescent granules are formulated to reduce these effects which are intended to be dissolved or dispersed in water before use. This dosage form includes a mixture which when incorporated in water produces an immediate rate of release of the therapeutic compound for instant release [2], Effervescent granules are popular delivery systems for many pharmaceutical products such as antacids, analgesics, and cough/cold formulations. They are fast dissolving, highly soluble, stable, convenient dosage forms. The granules are added into a glass of water just before administration and the drug solution or dispersion is to be drunk immediately. The granules are quickly dispersed by internal liberation of Carbon dioxide in water due to interaction between acid with alkali metal carbonates or bicarbonates in the presence of water [2].

Salbutamol sulfate is a bronchodilator that is beta- adrenergic agonist which stimulates beta adrenergic receptor. Salbutamol sulfate is indicated for the relief of bronchospasm for the management of asthma and reversible obstructive airway disease [3], Salbutamol sulfate is a white or practically white powder, with melting point range 180 °C, where it is freely soluble in water; slightly soluble in alcohol, in chloroform, and in ether, pKa 5.9, log P 1.0 and molecular weight 576.7 g/mole [4]. The structure of salbutamol sulfate is shown in figure 1.

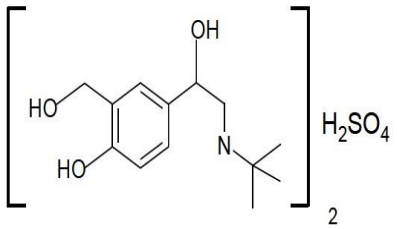


**Figure 1: Chemical structure of salbutamol sulfate [4]**

## Materials and methods

### Characterization of Salbutamol sulfate

- **Determination of melting point:** A small amount of Salbutamol sulfate powder is placed in a thin walled capillary tube 10-15 cm long, about 1 mm in inside diameter, and closed at one end , the melting point capillary was filled by pressing the open end into a small heap of salbutamol sulfate powder, turning the capillary open end up, and vibration it by drawing a file across the side to rattle the crystal down into the bottom and then positioned in electrical melting point apparatus and observed until complete melting of powder. Finally, the range of melting temperature is recorded [5].

- **Determination of λmax**: A standard stock solution is prepared by dissolving 100 mg of salbutamol sulfate in 50 ml of volumetric flask and dissolved in Distilled Water (DW) to obtain concentration 2 mg/ml (Standard stock I). Further, diluting 12.5 ml of stock solution to 25 ml with DW to get desired concentration of 0.5 mg/ml (Standard stock II). Appropriate amount of standard stock II solution was diluted with DW for spectral scan in the UV range of 400-200 nm to detect maximum wave length [6].

- **Preparation of calibration curve**: Adequate dilutions are made from standard stock solution (II) to obtain the concentration of 0.1, 0.08, 0.06, 0.04 and 0.02 mg/ml. The absorbance of each sample was plotted against its concentration [7].

**Formulation of salbutamol sulfate granules**

Effervescent granules of Salbutamol Sulfate (F1-F3), are prepared by the wet granulation method, the amount of acids and base are determined by stoichiometric calculation [8], it has been found that citric acid monohydrate, tartaric acid and sodium bicarbonate used in the ratio of 1:2:3.4, respectively. These calculated amounts are sufficient to prepare 500 gm of powder containing 2 mg of Salbutamol Sulfate as mentioned in Table 2. Salbutamol Sulfate(**Samarra, Iraq**), and all other excipients Citric acid (**Ludeco,Belgium)**,Tartaric acid (**Sigma®,USA**),Sodium bicarbonate (**DIDACTIC**), Polyvinylpyrrolidone(**Himedia®, India**), Mannitol (**Merck, Germany**) and Explotab 2%( **JRS PHARMA, Germany**) or Avecil 10%( **Fluka®, Germany**) are weighed accurately and mixed by geometric dilution to ensure proper distribution of drug in the powder mixture. Then sufficient amount of ethanol is added to make a damp mass. This mass is passed through sieve no 10 to get granules, these granules are dried in hot air oven at 40 °C then passed through sieve no 20, and finally they are packed in tightly sealed container.

**Table 2: Formulation composition of Salbutamol Sulfate effervescent granules per 500 mg**

| F No. | SS (mg) | PVP (mg) | Mannitol (mg) | C.A (mg) | T.A (mg) | $NaHCO_3$ (mg) | Explotab (mg) | Avecil (mg) |
|---|---|---|---|---|---|---|---|---|
| **F1** | **2** | **10** | **168** | **50** | **100** | **170** | | |
| **F2** | **2** | **10** | **158** | **50** | **100** | **170** | **10** | |
| **F3** | **2** | **10** | **118** | **50** | **100** | **170** | | **50** |

Where: (**SS**: Salbutamol Sulfate, **PVP**: Polyvinylpyrrolidone, **C.A:** Citric acid, **T.A:** tartaric acid, **$NaHCO_3$**: sodium bicarbonate).

**Evaluation of granules**

- **Particle Size Distribution:** The size distribution of the granules produced was determined by agitation for 10 min with a sieve shaker fitted [9]. With a progression of standard sieves. From the weight retained on each sieve, a particle size distribution graph was plotted from which the median diameter was determined.

- **Angle of repose:** Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. The frictional force in a loose powder or granules can be measured by angle of repose. It is an indicative of the flow properties of the powder [10-11]. $tan\ \theta = h/\ r$ ……. Equation. (1) Where, h is height of pile and r is radius of the base of pile.

The powder mixture was allowed to flow through the funnel fixed to a stand at definite height (H). The angle of repose was then calculated by measuring the height & radius of the heap of powder formed. Care was taken to see that the powder particles slip & roll over each other through the sides of the funnel.

**Table 3: Angle of repose as an indication of powder flow properties [10-11].**

| Angle of repose (degrees) | Type of flow |
|---|---|
| < 20 | Excellent |
| 20-30 | Good |
| 30-34 | Passable |
| > 40 | Very poor |

- **Bulk density:** 10 g granules blend introduced into a dry 25 ml graduated cylinder, without compacting. The granules were carefully leveled without compacting and the unsettled apparent volume, Vo was read. The bulk density was calculated using the following formula [12].

$$\rho_{bulk} = \frac{M}{Vo}$$ ……. Equation (2) Where, ρ bulk= Apparent bulk density, M =Weight of the sample, Vo = Apparent volume of powder.

- **Tapped density:** A suitable amount of granules was placed in a 25 ml measuring cylinder. After absorbing its initial volume, the sample was tapped 100 times then tapped volume, was measured, to the nearest graduated unit. Tapped density was calculated using equation [12].

$$\rho_{tab} = \frac{M}{Vf}$$ ……. Equation. (3), Where, $P_{tab}$= Tapped Density, M = Weight of the sample, V f= Tapped volume of powder.

- **Compressibility index (Carr's Index):** The flow ability of powder may be evaluated by comparing the bulk density (ρ bulk) and tapped density (ρ tab) of powder and the rate at which it packs down. The percentage of Carri's Index was calculated as [13].

$$Carr'sindex = \frac{\rho_{tab} - \rho_{bulk}}{\rho_{tab}} x\ 100$$ ……... Equation (4)**, Where**, $\rho_{tab}$ = Tapped Density, $\rho_{bulk}$ = Apparent bulk density

**Table 4: Carr's Index as an indication of powder flow [14].**

| Carr's index (%) | Type of flow |
|---|---|
| 5-15 | Excellent |
| 12-16 | Good |
| 18-21 | Fair to passable |
| 23-35 | Poor |
| 33-38 | Very poor |
| >40 | Extremely poor |

- **Hausner's ratio:** Hausner's ratio is an important character to determine the flow property of powder and granules. This can be calculation by the following formula [15].:

$$Hausner's\ ratio = \frac{\rho_{tab}}{\rho_{bulk}}$$ ..... Equation (5)**, Where**, $\rho_{tab}$= Tapped Density, $\rho_{bulk}$= Apparent bulk density.

**Table 5: Hausner's ratio [15].**

| Hausner's ratio | Type of flow |
|---|---|
| 1.00 – 1.11 | Excellent |
| 1.12 – 1.18 | Good |
| 1.19 –1.25 | Fair |
| 1.26 – 1.34 | Passable |
| 1.35 – 1.45 | Poor |
| 1.46 – 1.59 | Very poor |
| < 1.60 | Non-flow |

**In vitro Effervescence time**

In vitro effervescence time was measured by pouring the one dose of granules in a beaker containing 50 ml of Water [16]. Granules from each batch were randomly selected and in vitro effervescence time was measured.

**Amount of drug dissolved** A dose (500mg) of the effervescent granules is weighed accurately and added to 50 ml DW in an appropriate beaker. After 5 minutes, filtration was done with Millipore filter paper 0.45 μm. The filtrate was diluted with water and absorbance was measured at $\lambda_{max}$ of salbutamol sulfate. The concentration was calculated by applying calibration curve equation to determine the dissolved quantity of salbutamol sulfate [17].

**Results and discussion**

1. **Characterization of Salbutamol sulfate**

The melting point of salbutamol sulfate is found to be **180**°C which is similar to the reported in the literature [4]. These indicate the purity of drug powder.

The λmax of salbutamol sulfate is found to be **276** nm in water which agrees with the reported value in literature [18], as shown in figure 2.

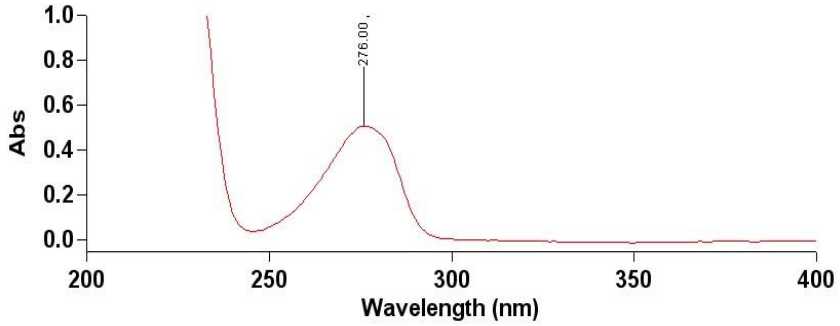


**Figure 2: UV- spectrum of Salbutamol sulfate in distilled water (λ max of salbutamol sulfate).**

A linear calibration curve of Salbutamol sulfate in water is obtained by plotting the absorbance at **276** nm against the corresponding Salbutamol sulfate concentration data as shown in Table 6. The calibration curve is shown in figure 3.

**Table 6: Absorbance data of Salbutamol sulfate**

| Concentration (mg/ml) | Absorbance (nm) |
|---|---|
| 0.1 | 0.507 |
| 0.08 | 0.3999 |
| 0.06 | 0.3178 |
| 0.04 | 0.186 |
| 0.02 | 0.0888 |

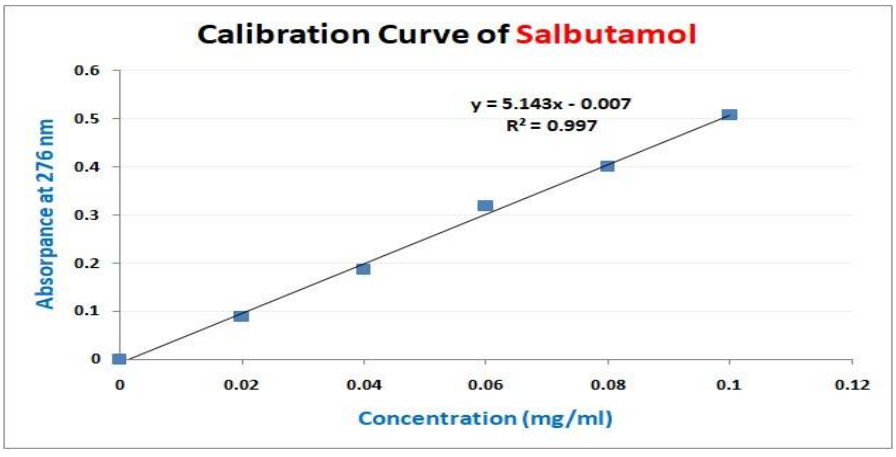


**Figure 3: Calibration curve of Salbutamol sulfate in water.**

## 2. Evaluation of Salbutamol Sulfate granules

- **Particle Size Distribution:** The analysis of particle size illustrates the maximum retention in the size range **425-150** μm for all formulations as shown in Figure 4. The mean diameter of the granules is found to be **0.3** mm approximately.

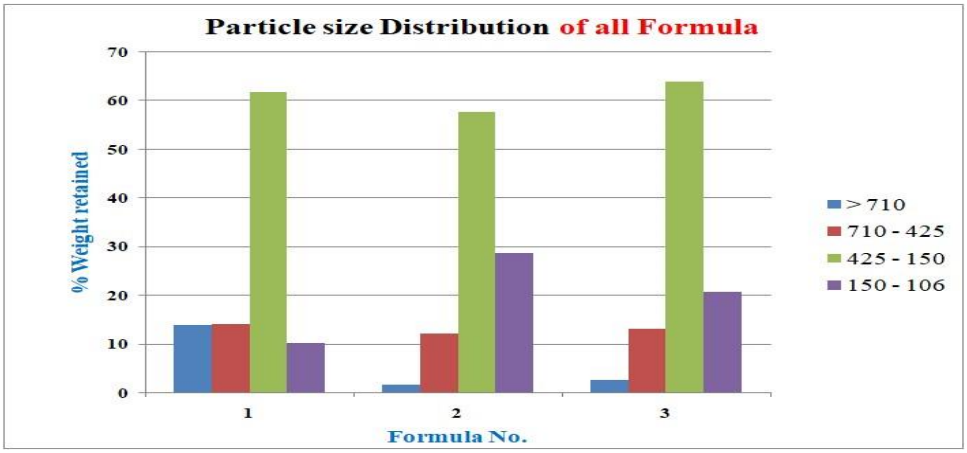


**Figure 4: Particle Size Distribution of all formula**

- **Flow property of the Salbutamol Sulfate granules**

The values for the angle of repose are found in the range of (26.29-29.42), these results are indicated good flow properties of all the prepared formulas. Bulk and tapped density of three formulas are measured, it was found that F3 with Avecil had higher bulk and tap densities as compared to F1 and F2.

The Carr's index and Hausner ratio are also calculated based on equations 4 and 5. The Carr's index and Hausner ratio are found to be lower (excellent flow properties) for F3 as compared to F1 and F2 due to Avecil have better flow properties. This is in accordance with density measurements. Carr's index is a measure of powder bridge strength and stability, and Hausner ratio is a measure of interparticular friction, lower Carr's index and Hausner ratio of a formula indicate better flow properties than higher ones. The above values are tabulated in Table 7.

**Table 7: Flow properties of Salbutamol Sulfate granules**

| F. No | Angle of repose (θ) | Pbulk | Ptab | Carr's index | Hausner's Ratio |
|---|---|---|---|---|---|
| $F_1$ | 26.29° | 0.454 | 0.526 | 13.68 | 1.15 |
| $F_2$ | 28.99° | 0.454 | 0.556 | 18.34 | 1.22 |
| $F_3$ | 29.42° | 0.526 | 0.571 | 7.88 | 1.08 |

- **Effervescence time and Amount of drug dissolved**
  1. The effervescence time is varied from one formula to other as shown in Table 8.

     Among all the formulations, F3 showed the least effervescence time (43 sec).

  2. The result of the Amount of drug dissolved for formula F3 shows that it is lower than other formulas.

**Table 8: effervescence time and Amount of drug dissolved**

| F. No | Effervescent time (sec) | Absorbance | Amount of drug dissolved |
|---|---|---|---|
| $F_1$ | 80 | 0.187 | 94.30% |
| $F_2$ | 84 | 0.174 | 87.98% |
| $F_3$ | 43 | 0.168 | 81.06% |

## Conclusion

Salbutamol Sulfate effervescent granules are prepared successfully by the wet granulation method containing citric acid and tartaric acid as acid components and sodium bicarbonate as a base source. Flowability and compressibility properties of the prepared salbutamol sulphate effervescent granules are accepted for both formulas contain either superdisintegrant (Explotab) or traditional one (Avecil).

Furthermore, there are some studies can be made on Salbutamol Sulfate effervescent granules and these are given as follows:

1- Furthers formulations variables such as sweeting, flavoring and coloring agents are recommended to study.
2- Stability study to determine expiration date.
3- Packaging types effect on stability.
4- Effect of humidity on storage conditions.

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