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# Formulation, development and evaluation of orally disintegrating tablets by sublimation technique

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**Abstract:** Asthma is defined simply as reversible airway obstruction characterized by attacks of breathlessness, tight chest, wheezing and coughing. The purpose of this investigation was to develop orally disintegrating tablets of terbutaline sulphate. Granules containing drug, diluent, subliming agents, aspartame were prepared by wet granulation technique using alcoholic solution of polyvinyl pyrrolidone K25 (10% w/v) as a binder. The dried granules were then mixed with lubricant magnesium stearate and glidant talc and compressed into tablets. Subliming agents was sublimed from the tablet by exposing it to drying at 65 $^0$C. The tablets were evaluated for percentage friability, hardness, weight variation, disintegration time and percentage drug content. Menthol containing tablets resulted in rapid disintegration as compared with tablets containing ammonium bicarbonate and camphor. Formulations F4 showed the minimum disintegration time of 16s. Formulations tested for all the official tests for tablets and were found to be within limits.

From the results, it was concluded that orally disintegrating tablets with terbutaline sulphate could be prepared by sublimation of tablets containing suitable subliming agent.

**Keywords:** Orally disintegrating tablets, terbutaline sulphate, sublimation, ammonium bicarbonate, menthol, camphor.

## Introduction

Asthma is defined simply as reversible airway obstruction. Asthma is a chronic disease that affects airways, characterised by attacks of breathlessness, tight chest, wheezing and coughing which are caused by the airways becoming narrowed and inflamed. The inflammation makes the airways very sensitive and patient tend to react strongly to things that are allergic to or find irritating. When the airways react, they get narrower and less air flows through the lung tissue. Signs of an asthmatic episode include wheezing, rapid breathing (tachypnea), prolonged expiration, a rapid heart rate (tachycardia), rhonchous lung sounds (audible through a stethoscope), over-inflation of the chest and anxiety about being unable to breathe. In a severe asthma attack, the airways can close so much that not enough oxygen gets to vital organs. This condition is a medical emergency. People can die from severe asthma attacks.[1-6] Asthma attacks can be caused by many things like exercise, cold air, allergies, and breathing in certain chemicals.

Asthma affects over 5-10% of population in industrialized countries. It afflicts approximately 53 million people across world mostly in United States, France, Germany, Italy, Spain, United Kingdom, and Japan. More than 4000 people die every year in India as result of complications arising from serious asthma attacks though there are several recommendations and treatments being reported.[7]

The treatment of asthmatic symptoms include inhalation therapy with metered dose inhalers with or without spacers, dry powder inhalers, and other aerosol systems; oral and injected medications. Oral administration is the most widely accepted route of delivery due to its ease of administration, convenience, versatility and most importantly patient compliance. Amongst them solid oral dosage forms represent the preferred class of products. The development of an appropriate dosage form for the elderly is most desirable due to the changes in various physiological functions associated with aging including difficulty in swallowing. Several new technologies for oral delivery have recently been available to improve patient compliance. One of these include orally disintegrating technology which offers the advantages of both solids and liquids such as quick disintegration and dissolution of tablets, no residue in mouth, requires no water intake, provides a pleasant mouth feel and even allows high drug load. The fundamental principle used in the development of the orally disintegrating tablets is to maximize its pore structure. Researchers have evaluated spray dried

materials[8] and plastic materials[9] for development of such tablets.

The aim of the present investigation is to develop orally disintegrating tablets taking terbutaline sulphate as a model drug to reduce the lag time and providing faster onset of action to relieve immediately acute asthmatic attack. In this study subliming agent is used to increase porosity of the tablets.

## Materials and Methods

Terbutaline sulphate (TS) was purchased from Melody Healthcare; microcrystalline cellulose was purchased from Nupur Herbals. Camphor and menthol were purchased from Laser Chemicals; ammonium bicarbonate was purchased from Merck Ltd.; mannitol and polyvinyl pyrrolidone K25 (PVP) was purchased from Loba chemie; magnesium stearate was obtained from Nikita Chemicals and Talc from S J Chemicals. All other ingredients used were of pharmaceutical grade.

**Preparation of terbutaline sulphate tablets:**

The raw materials were passed through a 100-mesh screen. Tablets were prepared by wet granulation process using sublimable components viz. camphor, menthol and ammonium bicarbonate. Six different formulations having different combination of sublimable excipients were prepared (Table **1**). Excipients were mixed with drug and this blend was granulated with non-aqueous granulating agent, polyvinyl pyrrolidone (PVP) in alcohol through sieve 44. The granules were air-dried and evaluated for granular properties. The dried granules were then mixed with lubricant magnesium stearate and glidant talc and compressed into tablets using flat face round tooling on a Rimek-I rotary tablet machine (Karnavati Eng. Pvt. Ltd, Ahmedabad). Tablets were subjected for drying at a temperature of 65 $^0$C for 24h to facilitate the volatilization of sublimable components added. The tablets were weighed at regular intervals until constant weight was achieved ensuring complete removal of the sublimable component.[10]

**Evaluation of formulated tablets:**

The crushing strength of the tablets was measured using a Monsanto hardness tester (Sheetal Scientific Industries, Mumbai, India). The friability of a sample of 20 tablets was measured using a Roche Friabilator (Veego, India). Twenty preweighed tablets were rotated at 25 rpm for 4 min. The tablets were then reweighed after removal of fines and the percentage of weight loss was calculated. For determination of disintegration time, one tablet was placed in each tube of disintegration apparatus (Veego, India). Disintegration test was carried out using distilled water as a disintegrating media at 37±2 °C.

Drug content was determined by dissolving a quantity of the powdered tablets containing 20 mg of TS with 50 ml of 0.1M sodium hydroxide for 10 minutes, diluted to 100 ml with 0.1M sodium hydroxide and filtered. Then 20 ml of this filtrate was further diluted to 50 ml with 0.1M sodium hydroxide and analyzed by UV spectrophotometer at 296 nm against blank prepared by using dummy tablets treated in a similar manner.

## Results and Discussion

Microcrystalline cellulose was used as a water insoluble diluent. Among the soluble diluents, mannitol was selected as a diluent considering its advantages in terms of easy availability and negative heat of dissolution. Aspartame was included in the formulation as a sweetener. Subliming agents such as ammonium bicarbonate, menthol and camphor were used to increase porosity of the tablets. Granules were prepared by wet granulation technique using alcoholic solution of PVP (10% w/v) as a binder. The granules were lubricated and compressed into tablets on a rotary tablet machine. PVP was used as a binder, considering its widespread applicability in the industry. Orally disintegrating tablets of TS could be prepared successfully using sublimable ingredients. Drying at 65 $^0$C rendered tablets porous by allowing the volatile components to escape through the tablet matrix. The tablets were found to be porous after drying thus facilitating their easier breakup in water. Tablets with lower friability ($\leq$0.9%) may not break during handling on machines and/or shipping. The use of a sublimating agent resulted in increased friability probably due to increased porosity.

Menthol containing tablets exhibited faster disintegration as compared with tablets containing ammonium bicarbonate and camphor. The porous structure is responsible for faster water uptake; hence it facilitates wicking action in bringing about faster disintegration. The formulation containing microcrystalline cellulose as filler showed minimum disintegration time which could be attributed towards disintegrating property of microcrystalline cellulose. However, the formulations containing mannitol as filler showed longer disintegration time, which could be, attributed to slower dissolution characteristics of mannitol. Also as mannitol is water soluble it tends to dissolve first before disintegration. All the prepared tablets were found to disintegrate fast showing disintegration time of less than a minute. Amongst the prepared formulations, F4 was found to have the minimum disintegration time of 16s. Formulations tested for all the official tests for tablets and were found to be within limits.

It is thus concluded that sublimation technique would be an effective alternative approach for orally disintegrating tablets preparation with a view of obtaining faster action of the drug and would be advantageous in comparison to the currently available conventional forms. The technique adopted was found to be economical and industrially feasible. TS being a water-soluble drug would be readily available in a dissolved form for rapid oral uptake. The rapid orally disintegrating concept in case of TS could be of a great importance in relieving acute asthmatic shocks.

**Table 1. Formulation and Evaluation of Orally disintegrating tablets.**

| Formulations | F1 | F2 | F3 | F4 | F5 | F6 |
|---|---|---|---|---|---|---|
| Ingredients (mg) | | | | | | |
| Terbutaline sulphate | 2 | 2 | 2 | 2 | 2 | 2 |
| Camphor | 12.5 | 12.5 | - | - | - | - |
| Menthol | - | - | 12.5 | 12.5 | - | - |
| Ammonium bicarbonate | - | - | - | - | 12.5 | 12.5 |
| Aspartame | 1 | 1 | 1 | 1 | 1 | 1 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 | 5 |
| Talc | 5 | 5 | 5 | 5 | 5 | 5 |
| PVP in alcohol | 5 | 5 | 5 | 5 | 5 | 5 |
| Microcrystalline cellulose q.s. | - | 20 | - | 20 | - | 20 |
| Mannitol q.s. | 20 | - | 20 | - | 20 | - |
| Parameter | | | | | | |
| Hardness (kg/cm$^2$) | 3.6±0.16 | 3.7±0.28 | 3.5±0.24 | 3.3±0.16 | 3.6±0.17 | 3.7±0.20 |
| Friability (%) | 0.4±0.10 | 0.7±0.08 | 0.7±0.08 | 0.9±0.05 | 0.5±0.06 | 0.7±0.11 |
| Weight variation (mg) | 50.1±0.431 | 49.7±0.63 | 49.8±0.51 | 48.7±0.33 | 49.1±0.68 | 50±0.46 |
| Disintegration time (sec.) | 53±1.31 | 44±1.0 | 20±1.20 | 16±1.11 | 26±1.18 | 19±1.16 |
| Drug content (%) | 98.6±0.11 | 97.8±0.24 | 98.8±0.33 | 98.1±0.22 | 98.8±24 | 97.9±0.12 |

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