

Orodispersible Tablets of Salbutamol Sulphate using combinational approaches for disintegration: For Effective Management of Asthma

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Citation

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Abstract

Asthma is an inflammatory disorder that results in the obstruction of air pathways and causes difficulty in breathing. Amongst the currently available means of treatment, conventional oral dosage forms are associated with lag time and delayed onset of action. Salbutamol sulphate is a selective β_2 receptor agonist widely used as bronchodilator and forms part of initial therapy in chronic as well as acute asthma. In present work an attempt has been made to formulate Orodispersible Tablets (ODT) of salbutamol sulphate by superdisintegrant addition and sublimation technique. ODTs containing subliming material were subjected to drying under vacuum to aid in sublimation and make tablets porous. It was concluded that tablets prepared by addition of sublimation method has less disintegration time than those prepared by superdisintegrant. These tablets give fast release of salbutamol sulfate which results in fast action in asthmatic attack.

INTRODUCTION

The treatment of asthmatic symptoms generally includes conventional oral dosage forms like tablets, capsules, oral liquids etc.; inhalation therapy includes metered dose inhalers with or without spacers, dry powder inhalers, and other aerosol systems. Oral administration is the most widely accepted route of delivery due to its ease of administration, convenience, versatility and most importantly patient compliance. Several new technologies for oral delivery have recently been available to address the problems of physicochemical and pharmacokinetic characteristic of drugs, while improving patient compliance. One of these include orodispersible tablet 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 loading.

An attempt was made for preparation of orodispersible tablets of a model bronchodilator, salbutamol sulphate with an aim of reducing the lag time and providing faster onset of action to relieve immediately acute asthmatic attack. This would be advantageous as conventional solid oral dosage forms are often associated with a longer lag time and thus slower onset of action, while oral liquids prove to have faster

onset of action but require careful handling. Aerosol systems are specific but fail to deliver the actual dose of drug with only ten percent of administered dose deposited on the bronchi while rest of the drug is deposited in oropharynx and is swallowed. Also, metered dose system are less portable while dry powder inhalers cause clogging of device and require skillful operation. An orodispersible tablet form would thus be advantageous, as salbutamol sulphate is water-soluble drug and its formulation into an orodispersible tablet form would render it to disintegrate rapidly and thereby result in rapid absorption without any lag time.

Commercially available ODT's are prepared by various techniques, mainly lyophilization, molding and direct compression. The lyophilization and molding techniques produce ODTs which have low physical resistance and high friability. On the other hand, tablets obtained by direct compression are less friable with good disintegration properties. The simplicity and cost effectiveness of the direct compression process have positioned it, as an attractive alternative to traditional granulation technologies.

In the present study an attempt has been made to prepare Orodispersible tablet, which disintegrates in oral cavity in less than one minute using combination of superdisintegrant

and subliming agents, with sufficient mechanical strength.

MATERIAL AND METHOD

Salbutamol sulphate was obtained as a gift sample from Cipla Pharma R & D, Vikhroli. Microcrystalline cellulose (Avicel pH 102) and Crosspovidone were obtained as gift sample from Signet Chemical, Mumbai. Camphor, Menthol, Thymol and Ammonium bicarbonate were purchased from Merck Ltd, Mumbai. Magnesium stearate and Talc were purchased from S. D. Fine Chemicals, Mumbai.

PREPARATION OF BLENDS

All the ingredients (shown in Table 01) were passed through mesh number 60, and they were co-ground and mixed properly together in a pestle motor for 15 minutes. Talc and Magnesium stearate were mixed at the end of the process.

EVALUATION OF BLEND

There are many formulations and process variables involved in mixing step and all these can affect the characteristics of blend produced. These blends were evaluated for mass-volume relationship (Bulk Density, Tapped Density, Hausner's Ratio, Compressibility Index) and flow properties (Angle of Repose).

The bulk density and tapped density of the mixed powders before compression were studied for determining the Hausner's ratio (H) and Carr's index (I %) from a known weight of sample using a measuring cylinder and following formula⁶⁷⁸ :

{ image:1 }

Where, ρ_t = Tapped density

ρ_b = Bulk density

Angle of Repose was determined using funnel method. The blend was poured through a funnel that can be raised vertically until a specified cone height (h) was obtained. Radius of the heap (r) was measured and angle of repose (θ) was calculated using the formula:

{ image:2 }

Where, θ = Angle of Repose, h = height of cone, r = radius of cone

{ image:3 }

COMPRESSION OF TABLETS

The mixed blend of excipients were compressed using a single punch tablet punching machine (Cadmach, Ahmedabad) to produce flat faced tablets weighing 100 mg each with 7 mm diameter. A minimum of 100 tablets were prepared for each batch.

EVALUATION OF TABLETS

After compression of powder, the tablets were evaluated for organoleptic and physical characteristics like color, odor, taste, diameter, thickness, weight variation, hardness and friability. Tablets were also evaluated for In vitro disintegration time, wetting time and In vitro dispersion time. In vitro dissolution studies of orodispersible tablets and conventional marketed formulation were carried using 900-mL Sorenson's buffer (pH 6.8) as the dissolution media.

TABLET THICKNESS

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using digital micrometer (Mityato, Japan).

WEIGHT VARIATION

USP 2004, procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance (Shimadzu, Japan). The average weight of one tablet was determined from the collective weight.

HARDNESS

The tablet crushing load, which is the force required to break a tablet by compression in the radial direction, was measured using a Monsanto hardness tester (Tab-Machines Ltd., India). The test was performed on 10 tablets and the average was calculated.

FRIABILITY

Friability of the tablets was determined using Roche Friabilator (Electrolab, India). This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Prewighed sample of 20 tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F %) is given by the formula

{image:4}

Where, W_1 is weight of the tablets before the test and W_2 is the weight of the tablets after test.

DRUG CONTENT

Five tablets were powdered and the blend equivalent to 4 mg of Salbutamol sulphate was weighed and dissolved in suitable quantity of Sorensen's buffer pH 6.8. Solution was filtered, diluted and drug content analyzed spectrophotometrically at 276 nm.

IN VITRO DISINTEGRATION TEST

Disintegration of orodispersible tablets is achieved by saliva in the mouth, however amount of saliva in the mouth is limited and no tablet disintegration test was found in USP and IP to simulate in vivo conditions. A modified version of the simple but novel method developed was used to determine disintegration time of the tablets. A cylindrical vessel was used in which 10-mesh screen was placed in such way that only 2 ml of disintegrating or dissolution medium would be placed below the sieve (Fig. 1). To determine disintegration time, 6ml of Sorensen's buffer (pH 6.8), was placed inside the vessel in such way that 4ml of the media was below the sieve and 2ml above the sieve. Tablet was placed on the sieve and the whole assembly was then placed on a shaker. The time at which all the particles pass through the sieve was taken as a disintegration time of the tablet. Six tablets were chosen randomly from the composite samples and the average value was determined¹⁰.

{image:5}

WETTING TIME

A piece of tissue paper (12 cm X 10.75 cm) folded twice was placed in a small Petri dish (i. d. = 6.5 cm) containing 6 ml of Sorensen's buffer (pH 6.8). A tablet was placed on the paper, and the time for the complete wetting was measured (Fig. 2). The test was carried out on triplicate and the mean value was considered¹¹.

{image:6}

IN VITRO DISPERSION TIME

Tablet was added to 10ml of Sorensen's buffer solution (pH 6.8) and time required for complete dispersion was measured. Three tablets from each formulation were randomly selected and in vitro dispersion time was performed¹².

{image:7}

IN VITRO DRUG RELEASE

In vitro dissolution studies for all the fabricated tablets was carried out using USP paddle method at 50 rpm in 900 ml of Sorensen's buffer (pH 6.8) as dissolution media, maintained at $37 \pm 0.5^\circ$. 5 ml aliquot was withdrawn at the specified time intervals, filtered through whatmann filter paper and assayed spectrophotometrically at 276 nm. An equal volume of fresh medium, which was prewarmed at 37°C was replaced into the dissolution media after each sampling to maintain the constant volume throughout the test. Dissolution study of conventional marketed tablet of salbutamol sulphate is also carried out using same method¹³.

STABILITY PERFORMANCE

The stability of selected formulation was tested at different stress conditions ($30 \pm 2^\circ\text{C} / 65 \pm 5\% \text{RH}$ and $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$) for one month following open dish method. At the end of each 7 days, tablets were tested for thickness, weight, hardness, friability, In-vitro disintegration time, wetting time and dispersion time¹⁴.

RESULT AND DISCUSSION

EVALUATION OF BLENDS

For each formulation blend of drug and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.574-0.627 g/cm^3 and tapped density between 0.655-0.718 g/cm^3 as shown in Table 01. Using this data, compressibility index and hausner's ratio was calculated. The powder blends of all the formulations had compressibility index between 10.101 and 14.648 which indicated good flowability of the powder blend. Hausner's ratio for all formulation was less than 1.2, indicating good flowability. The good flow characteristics were also exhibited by the values of angle of repose for the blends that ranged from 21.376 - 26.108. The results are shown in Table 01.

EVALUATION OF TABLETS

Since the powder material was free flowing, tablets were obtained of uniform weight due to uniform die fill, with acceptable weight variations (percentage deviation was within $\pm 10\%$) as per pharmacopoeial specifications. Thickness of tablets was found between 2.228 and 2.421. This indicates that the materials behaved uniformly throughout the compression process. Hardness of tablets was found out to be 2.615-3.230, sufficient to withstand mechanical shock.

The friability problem occurred with the formulations prepared by using sublimation method alone. Tablets were more friable and the friability of batch containing menthol (ODT3) was found to be about 0.9%. All the parameters were found within the specified limit for uncoated tablets.

The most important parameter that needs to be optimized in the development of ODTs is disintegration time of tablets. The disintegration time of the tablets prepared by using either sublimation method or superdisintegrant addition was found in the range of 51.66-72.33 s and wetting time was found in the range of 46.66-77.33 s, except ammonium bicarbonate which disintegrates in 131.66 s. Dispersion time for these formulations was found within 60.66-81.33 s, except ammonium bicarbonate.

On the other hand, it was found that all these parameters improved in case of tablets prepared with combination of superdisintegrant and subliming agent. These formulations (ODT6-ODT9) disintegrated faster in 11.66-34.00 s. The formulation designated as ODT6 was found out to be the best as this formulation showed least disintegration time of 10.33 sec, short wetting time and good content of active ingredient. The porous structure resulted owing to sublimation was responsible for faster water uptake; hence it facilitated wicking action of croscopolvidone in bringing about faster disintegration. These formulation shows also benefit in term of friability. The results have been tabulated in table 02.

{image:8}

In vitro dissolution studies (Figure 04) for ODT confirmed the results obtained with simple and tablets using combination of superdisintegrants and subliming agents. Significant rapid release of drug from the formulated tablets was observed 40.49-65.92 % for simple tablets (ODT1-ODT5) and 84.45-99.40% for combination tablets (ODT6-ODT9). Tablets containing combination release above 84% of the drug at the end of 5 min, which may be attributed to rapid burst effect produced by excipients.

{image:9}

Stability study was conducted for the optimized batch. There was no significant color and odor change and no significant variation in the in vitro dispersion time, wetting time, and in vitro dissolution profiles after one month of stability studies for the formulations at 30±2 C /65±5% RH and 40°C/75% RH.

Comparison of tablets prepared by superdisintegrants addition and sublimation method separately and with combination technique revealed that combination technology was superior to either of these methodologies alone.

CONCLUSION

It was concluded that orodispersible tablets can be successfully prepared with a view of obtaining faster action of the drug and would be advantageous in comparison to the currently available conventional forms. Salbutamol sulphate being a water-soluble drug would be readily available in a dissolved form for rapid oral uptake. The rapid dissolving concept in case of salbutamol sulphate could be of great importance in relieving acute asthmatic attacks. The technique was found to be economically and industrially feasible.

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