FORMULATION AND EVALUATION OF FAST DISINTEGRATING TABLET OF SALBUTAMOL SULPHATE

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ABSTRACT

INTRODUCTION

When put on the tongue, fast dissolving tablets immediately dissolve, often in a matter of seconds. They do not need any additional water to make them easier to swallow. Salbutamol sulphate fast disintegrating tablets have a higher bioavailability and dissolving rate.

MATERIAL AND METHODS

This experimental study was conducted in the Pharmaceutic laboratory of Department of Pharmacy at Universal College of Medical Sciences, Bhairahawa, Nepal from February 2022 to July 2022. A tablet was created utilizing the direct compression method employing mannitol as a diluent and various quantities of super disintegrants, including sodium starch glycolate, croscarmellose sodium, and PVPK-30 as a binder. Pre-compression and post-compression parameters for the formulation were evaluated.

RESULTS

When examined for hardness, thickness, weight variation, in vitro disintegration time, drug content, and in vitro drug release, tablets were determined to be adequate. Among all formulations, F6 showed that its disintegration time is least and in-vitro dissolution test depicts that F6 formulation shows the maximum drug release (99.99%) within 30 minutes.

CONCLUSION

This study brings the effectiveness in dosing of patients who have problem in swallowing of conventional dosage form. Among formulations, 15 mg of croscarmellose sodium was found to be the best.

KEYWORDS

Fast disintegrating tablet, Direct compression method, Salbutamol sulphate

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https://doi.org/10.3126/jucms.v12i02.69619

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INTRODUCTION

The oral route of administration is the most popular because of its numerous advantages, including convenience of administration, precise dosage, self-medication, pain avoidance aversion, adaptability, and patient compliance.[1] The orally fast-disintegrating tablet is one of the most extensively used commercial items among the dose forms intended to make treatment easier. FDTs are useful in patients who have difficulty swallowing conventional tablets, capsules, and liquid orals or syrups, such as pediatric, geriatric, bedridden, or developmentally disabled patients, resulting in ineffective therapy, persistent nausea, sudden episodes of allergic attacks, or coughing for those who have an active lifestyle.[2,3]

Recent innovations in novel drug delivery system aim to improve drug molecule safety and efficacy by producing a convenient dosage form for ease of administration and improved patient compliance.[4]

Orally disintegrating tablets are solid dosage forms containing medical drugs that disintegrate quickly, usually within seconds, when placed on the tongue, and do not require additional water to facilitate ingestion.[5] The bioavailability may be enhanced through oral cavity absorption as well as pre gastric absorption of saliva containing dispersed medicines that move down into the stomach. Furthermore, when compared to normal tablets, the amount of medication susceptible to first-pass metabolism is reduced.[6] European Pharmacopoeia described ODTs as "uncoated tablets intended to be placed in the mouth where they disperse rapidly before being swallowed" and as tablets which should disintegrate within 3 minutes.[7,8] The United States Food and Drug Administration and Center for Drug Evaluation and Research drafted guidance which states ODTs as 'a solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue.[9] Salbutamol sulphate is a selective β2 - receptor agonist widely used as a bronchodilator to relieve acute asthma and chronic obstructive pulmonary disease.[10,11] Oral Salbutamol undergoes hepatic metabolism and bioavailability is 50%, duration of action is 4-6 hours.[12]

MATERIAL AND METHODS

Salbutamol Sulphate was received as gift sample from Siddhartha Pharmaceuticals Pvt. Ltd, Madhawaliya, Rupandehi, Nepal. Ethical clearance was obtained from Institutional Review Committee having Reference No. UCMS/IRC/039/22 on February 8, 2022.

The excipients in the formulation were salbutamol sulphate as active pharmaceutical ingredient, sodium starch glycolate and croscarmellose as super disintegrant, mannitol as diluent, magnesium stearate as lubricant, talcum as glidant, PVPK-30 as binder, aspartame as sweetening agent, disodium hydrogen phosphate and potassium dihydrogen phosphate as buffer.

The equipments used in the formulation were electronic balance, UV visible spectrophotometer, digital pH meter, hot air oven, hardness tester, friability test apparatus, disintegration test apparatus, dissolution test apparatus and tablet compression machine.

Preparation of standard stock solution of salbutamol sulphate

10 mg of salbutamol sulphate was accurately weight and transfer to 100 ml of volumetric flask and was dissolve in the buffer having pH of stimulated saliva (6.8) to 100 ml. Further 0.1 ml of this solution was pipette out and volume was made up to 10 ml with buffer to prepare solution containing (0.1µg/ml) of the salbutamol sulphate.

Similarly, 2, 4, 6, 8, 10 µg/ml of salbutamol sulphate was prepared and absorbance of each standard stock solution was read out by the help of UV spectroscopy at 276 nm to obtained calibration curve. This curve helps to determine the concentration of the unknow sample by comparing the standard stock sample of known concentration.

Preparation of buffer pH 6.8 (stimulated saliva pH)

Take 28.80g of disodium hydrogen phosphate and 11.45g of potassium dihydrogen phosphate and finally dissolve in 1000 ml of distilled water.

Preparation of fast disintegrating tablet of salbutamol sulfate by direct compression method (Table 1)

Weigh all the ingredients accurately and then pass through the sieve 80# and keep it in a hot air oven to make them anhydrous. Initially the mannitol and API were mixed homogeneously then other excipients except magnesium stearate and talc were mixed thoroughly. The mixed blends were finally lubricated with magnesium stearate and then pass through the hopper using talc as a glidant and finally, the tablet was formulated by direct compression method using an eight-station compression machine.

Table 1. Formulation of FDTs of salbutamol sulphate

Materials	F1	F2	F3	F4	F5	F6
Salbutamol sulphate	2	2	2	2	2	2
Sodium starch glycolate	5	10	15	-	-	-
Croscarmellose sodium	-	-	-	5	10	15
Talc	5	5	5	5	5	5
Magnesium stearate	7	7	7	7	7	7
Aspartame	5	5	5	5	5	5
Mannitol	171	166	161	171	166	161
PVPK-30	5	5	5	5	5	5
Total weight (mg)	200	200	200	200	200	200

RESULTS

Evaluation of pre-formulation parameter

Bulk density

It can be calculated by pouring the power into a measuring cylinder, initial weight will be noted. This initial volume is called bulk volume. The bulk density is the ratio of mass of powder to bulk volume. The maximum bulk density was found to be 0.483 g/cm^3 for F6 and minimum was found to be 0.445 g/cm^3 for F3.

Tapped density

Tapped density was measured by transferring a known quantity of blend into a graduated cylinder. The tapped density is defined as the ratio of mass of powder blend to the Tapped volume of powder. After filling measuring cylinder transfer to the apparatus and tapped for 100 times. The maximum tapped density was found to be 0.586 g/cm^3 for F6 and minimum was found to be 0.487 g/cm^3 for F3.

Carr's index
Its measured by using following equation; carr's index (%) = $[(D_t-D_b)/ Dt]\times100]$
Where, D_t= tapped density, D_b= Bulk density of powder
The maximum Carr's index was found to be 17.566 % for F6 and minimum was found to be 9.000% for F3. The value below the 16% indicate a powder which usually give rise to the good flow properties whereas above 23% indicate poor flow properties.

Angle of repose
The funnel method was used to estimate the angle of repose of mixes. In a funnel, the precisely weighed blend was placed. The funnel's height was modified such that the tip of the funnel was barely touching the apex of the mix heap. The mixture was allowed to pour freely on the surface from the funnel. The heap created by the blend's diameter and height were measured. The angle of repose was determined using the formula below:
Tan (θ) = h/r
Where, θ= angle of repose, h= height(cm), r=radius(cm)
The maximum angle of repose was found to be 31.89° for F6 and whereas minimum angle of repose was found to be 27.69 for F3.

Hausner's ratio
It can be calculated by following formula. Hausner's ratio = D_t/D_b
Where, D_t= Tapped density
D_b= Bulk density of powder
The maximum value found to be 1.218 in F6, and minimum value was found to be 1.110 in F2. Powder having the Hausner's ratio less than 1.5 indicates good flow properties.[13]

Evaluation of post-formulation parameter

Thickness of tablet[14]
The thickness of tablet was measured by Vernier caliper. Now the extension of deviation from standard deviation can be measured. The % variation controlled within the standard value.

10 tablets from each batch were taken randomly and thickness was evaluated with their average and percent deviation. Maximum thickness (3.62±0.02) was found in F4 whereas minimum thickness (3.54±0.036) was found in F5 formulation (Table 2).

Weight variation[15]
Take 20 tablet and weight individually. Calculate average weight.
%Weight variation=(Individual wt.-average wt.)/average wt.) ×10

20 tablets from each batch were taken randomly and were accurately weight on an analytical balance. Maximum weight variation (203.8±0.405) was found in F1, and minimum weight variation (201±0.192) was found in F6 formulation (Table 2).

Friability[16]
Friability of tablet can be determined in lab by using Roche Friabilator. It consists of plastic chamber that revolve at 25 rpm and tablet drop from a distance of 6 inches in Friabilator, which rotate at 100 revolutions. Tablet were de-dust using muslin cloth and again weight. Weight loss should not be more than 1%.

$$\text{Friability (\%)} = \frac{Wi-Wf}{Wi} \times 100$$

10 tablets from each batch were taken randomly and friability was evaluated with their average. The maximum friability (0.7) was found in F3 and minimum friability (0.3) was found in F1 formulation. (Table 2)

Hardness[17]
It is defined as the force required to break a tablet in diametric compression. It is measured by using Monsanto and Pfizer tablet hardness tester.
Hardness for FDTs tablet = 2-3 kg/cm^2

3 tablets from the batch were taken randomly and hardness was evaluated with their average and percent deviation. The maximum hardness (3.00±0.16) was found in F1 whereas minimum hardness (2.67±0.10) was found in F3 formulation (Table 2).

Wetting time[18]
In a small petri dish (6.5 cm) holding 6 ml of pH 6.8, a piece of tissue paper folded twice was inserted (simulated saliva fluid). On the paper, a tablet was placed, and the time for complete wetting was measured.

In a small petri dish holding 6 ml of pH 6.8, a piece of tissue paper folded twice was inserted (simulated saliva fluid). On the paper, a tablet was placed, and the time for complete wetting was measured. The maximum wetting time 65 sec was found in F1 and minimum wetting time (25.85 sec) was found in F6 formulation (Table 2).

Disintegration time[19]
Six tablets were chosen at random from each batch. The test was performed using a tablet disintegration test device from the United States Pharmacopeia.

Place one tablet in each tube and the tube is move up and down 28-32 cycle/min. temperature maintains at 37±2°c.When all of the particles had gone through the screen, the tablet was declared entirely dissolved. Individual tablet disintegration periods were collected, and the average SD is presented.

The maximum disintegration time (130±3.55) was found in F3 and minimum disintegration time (30±0.81) was found in F6 formulation (Table 2).

Drug content uniformity[20]
Ten tablets (200 mg) were powdered in a mortar pestle, and the blend equivalent to 2 mg of salbutamol sulphate was weight and dissolved in 100 ml of 6.8 pH phosphate buffer solution. The solution was sonicated, filtered through Whatman filter paper, and suitably diluted with 6.8 pH buffer solution, and the drug content was analyzed by using a double beam UV spectrophotometer at 276 nm respectively. Each sample was analyzed in triplicate.

Percentage was found in range and shows good content of uniformity among the prepared formulation. Formulation F1 show maximum 102.3 % of assay whereas formulation F4 show the minimum 96.5% assay (Table 2).

In-vitro dissolution study[21]
Six tablets of each test and reference formulation were put in a dissolving apparatus (USP Apparatus-II: Paddle Stirring Element) holding 500 mL of dissolution medium at 37± 0.5C° and 50 rpm. Multiple points sampling was carried out in phosphate buffer pH 6.8. At 5, 10, 15, 20, 30 minutes and a 10 ml sample were extracted and replaced with fresh 10 ml of the same solution. Each test and reference solution were diluted, filtered, and spectrophotometrically at 276 nm examined.

In-vitro dissolution test (Table 3) (Figure 1)

6 tablets of salbutamol sulphate were put in a dissolving apparatus holding 900 ml of dissolution medium at 37± 0.5C° and 50 rpm. Multiple points sampling was carried out in phosphate buffer pH 6.8. At 5, 10, 15, 20, 30 minutes and a 10 ml sample were removed and replaced with fresh 10 ml of the same solution. Each test and reference solution were diluted, filtered, and spectrophotometrically examined at 276 nm.

Table 2. Post formulation parameters

Formulation	Weight variation (mg)	Hardness (mm)	Thickness (mm)	Friability (%)	Disintegration Time (sec)	Drug content %	Wetting time (sec)
F1	203.8±4.05	3.00±0.16	3.58±0.026	0.3	55±0.94	102.3	65
F2	201.95±2.78	2.83±0.24	3.57±0.024	0.6	130±3.55	98.3	27.19
F3	201.55±3.02	2.67±0.10	3.59±0.012	0.7	43.33±1.24	101.2	35.78
F4	200.85±2.49	2.75±0.14	3.62±0.021	0.5	36±1.24	96.5	28.95
F5	202±1.92	2.83±0.16	3.54±0.036	0.4	48±0.81	101.2	36.26
F6	201±1.92	2.86±0.13	3.60±0.033	0.5	30±0.81	98.4	25.85

Table 3. Dissolution profile for various formulations

Time (min.)	F1	F2	F3	F4	F5	F6
5	61.86	57.1	53.2	62.18	65.2	69.2
10	66.55	64.2	61.3	69.91	74.3	80.4
15	73.2	72.4	69.8	75.2	88.2	89.3
20	81.1	86.1	75.4	82.16	91.6	92.1
25	90.3	92.3	86.5	91.6	96.4	97.5
30	97.1	96.5	95.2	97.8	98.7	99.9

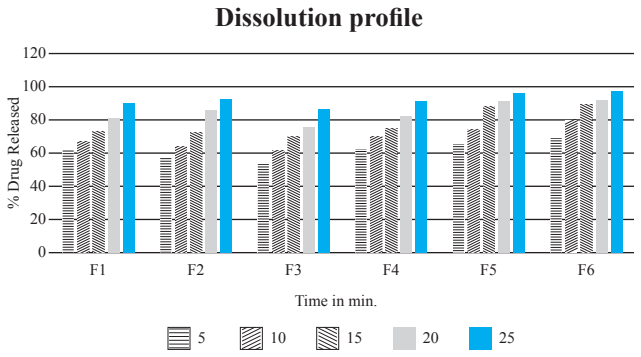

Figure 1. Comparative bar diagram of dissolution profile of F1-F6

DISCUSSION

Different formulations of fast dissolving tablet of salbutamol sulphate were prepared by direct compression method using different concentration of super disintegrants e.g. sodium starch glycolate and croscarmellose sodium. Mannitol was used directly compressible diluent, aspartame used to enhance the palatability, PVPK-30 use as binder, magnesium stearate and talc used to improve the flow properties.[22]

Super disintegrants are mainly used in the preparation of fast disintegrating tablet for the increment in the drugs solubility, croscarmellose sodium is a modified cellulose, internally cross-linked polymer of carboxymethyl cellulose. The effective concentration is (1-5 %) w/w, normally (1-3 %) is used in direct compression method. Sodium starch glycolate rapidly absorbed water from medium that may lead to fast disintegration. It is used in concentration between (2-8 %) w/w. Higher concentration above the 8% show the increase in disintegration time due to gelling and its subsequent viscosity producing effect.[23]

After the blending, the powder was subjected to evaluation of various pre-formulation parameter such as bulk density, tapped density, angle of repose, carr's index and hausner's ratio. The evaluation parameters were found in acceptable limit. The powder was compressed and various post formulation parameter were evaluated.

The maximum hardness was found in F1 due to the high packing fraction. The friability was also found within the limit i.e. NMT 1%. Tablets produced were of uniform weight with acceptable weight variation in the range from 200.85 mg to 203.8 mg due to uniform die fill. Hardness (2-3 kg/cm^2) indicated that tablets had a good mechanical resistance.

The tablet was evaluated for the in-vitro disintegration time formulation F6 containing 15mg of croscarmellose sodium show the disintegration time 30±0.81 sec which is the lowest among all formulation. This is due to the rapid uptake of water from the medium, swell in two dimension and disintegrate rapidly. Disintegrating time of SSG is high when concentration increased its due to gelling and its subsequent viscosity producing effect. There is direct correlation between wetting time and disintegrating time.

Dissolution process depend upon the wetting time followed by the disintegration of tablet. It was observed that percentage drug release increased with increased concentration of CCS and decrease with increase the concentration of SSG. This may be due to the reason that tablet prepared with SSG disintegrate due to the rapid uptake of the medium followed by rapid swelling but release drug slowly due to the formation of viscous gel.[24]

CONCLUSION

It was concluded that the super disintegrants based fast dissolving tablet of salbutamol sulphate would be quite effective by providing quick onset of action without need for water for swallowing or administration. The tablet disintegrates rapidly in oral cavity and had acceptable hardness and friability. In vitro drug release shows the significantly improved drug dissolution.

CONFLICT OF INTEREST

None

ACKNOWLEDGEMENT

I would like to express my humble gratitude to Ashish Lamsal and Roshan Kumar Mehta for sharing expertise, sincere and invaluable guidance. I also express my sincere gratitude to my respected seniors for their support, advice and guidance during my research work, and study period.

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