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Comparison of different superdisintegrants in designing of fast dissolving tablets of salbutamol sulphate

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ABSTRACT

Salbutamol Sulphate is a selective β2 receptor agonist widely used as a bronchodilator which is used for the treatment of asthma. The purpose of this research was to develop fast disintegrating tablets of Salbutamol Sulphate using super disintegrating agents. Recently fast disintegrating drug delivery system have started gaining popularity and acceptance as new drug delivery system, because they are easy to administer and lead to better patient compliance. In present work an attempt has been made to formulate and evaluate fast disintegrating tablets of Salbutamol Sulphate. Croscarmellose sodium, sodium starch glycolate and Indion 414 were used as super disintegrating agents, while microcrystalline cellulose and mannitol were used as diluents. Direct compression technique was used as it requires conventional tablet machinery and thus economical process. Formulations were evaluated for precompressional parameters such as angle of repose, % compressibility and Hausner's ratio. The prepared tablets were evaluated for post compressional parameters such as hardness, friability, thickness, Weight Variation, Uniformity of Content (%), in-vitro dispersion time, Amount of drug release. Formulations containing Indion 414 as super disintegrating agent show rapid in-vitro dispersion time as compared to other formulations.

Keywords: Salbutamol sulphate, croscarmellose sodium, sodium starch glycolate, Indion 414, microcrystalline cellulose.

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INTRODUCTION

Now a day fast dissolving tablets are gaining more importance in the market. Currently these tablets are available in the market for treating many disease conditions. More is concerned on hypertension[1], migraine[2], dysphasia[3], nausea and vomiting[4], Parkinson's disease[5], schizophrenia[6], pediatric emergency[7]. These conditions are those which require the drug to be formulated as fast dissolving tablets. Some patient prefers fast dissolving tablets to conventional tablets best of ease of administration, swallowing, pleasant taste and the availability in several flavors[8]. The pediatric and geriatrics patients are of particular concern. To overcome this, dispersible tablets[9] and fast-disintegrating tablets[10] have been developed. Most commonly used methods to prepare these tablets are; freeze-drying/Lyophilization[11]. Molding[12] and direct-compression methods[13]. Lyophilized tablets show a very porous structure, which causes quick penetration of saliva into the pores when placed in oral cavity. The main disadvantages of tablets produced are, in addition to the cost intensive production process, a lack of physical resistance in standard blister packs and their limited ability to incorporate higher concentrations of active drug. Moulded tablets dissolve completely and rapidly. However, lack of strength and taste masking are of great concern. Main advantages of direct compression are low manufacturing cost and high mechanical integrity of the tablets. Therefore, direct-compression appears to be a better option for manufacturing of tablets. The main objective of present work was to develop fast dissolving MT tablet by direct compression method and to study the effect of functionality differences of superdisintegrants on the tablet properties.

Dysphasia or difficulty in swallowing of the most popular dosage form like tablets and capsules is the major problem occurring in geriatric and pediatric patients, which leads to patient non-compliance[14]. Salbutamol Sulphate which is β2 receptor agonist widely used as bronchodilator to relieve acute as well as chronic attacks of asthma was selected as drug candidate as it is not available in such a dosage form [15,16]. The aim of this study was to develop such NDDS for Salbutamol Sulphate by simple and cost effective direct compression technique.

Thus, melt-in-mouth DDS are fast dissolving/ dispersing DDS, which dissolve in patient's mouth within a few seconds without the requirement of water, or chewing, providing best remedy for the patients suffering from dysphasia. Some drugs are absorbed from mouth, pharynx and esophagus as the saliva passes down the stomach. In such cases the bioavailability is greater than those observed for conventional dosage form. The advantages of mouth dissolving dosage form are increasingly being recognized in both industry and academia.

MATERIALS AND METHODS

Salbutamol Sulphate was gifted by Cipla Labs. Ltd. Mumbai. Directly compressible microcrystalline cellulose (MCC), croscarmellose sodium (CCS), crospovidone (CP), sodium

starch glycolate (SSG), Indion 414, were obtained from Cipla Pharma. Ltd. Vikroli, Mumbai. Other reagents were of analytical grade.

Preparation of fast dissolving tablets of salbutamol sulphate by direct compression method:

Fast dissolving tablets of SS were prepared by direct compression. All the ingredients were passed through 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 200mg using 8mm round flat punches on 10-station rotary tablet machine (Rimek). A batch of 30 tablets of each formulation was prepared for all the designed formulations. Different formulations compositions are given in **(Table 1)**

Evaluation of Mixed Powder Blend of Drug and Excipients:

Angle of repose

It is the maximum angle that can be obtained between the freestanding surface of a powder heap and horizontal plane. Such measurement gives at least a qualitative assessment of internal cohesive and frictional effects under low levels of external loading, as might apply in powder mixing or in tablet die or capsule shell filling operation. Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, H was obtained. Diameter of heap, D, was measured. The angle of repose was calculated by the formula [17]

$$\text{Tan } \theta = h/r$$

Where h and r are the height and radius of the powder cone.

Bulk density

Apparent bulk density was determined by pouring pre-sieved (40 sieve) bulk drug into a graduated cylinder via a large funnel and measuring the volume and weight “as it is” [17].

Tapped density

It is determined by placing a graduated cylinder containing a known mass of drug or formulation on mechanical tapping apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum13. Using the weight of drug in cylinder and this minimum volume, the tapped density may be computed[17]

Porosity

Ratio of total volume of void spaces to (Vv) to the bulk volume of material is often selected to monitor the progress of compression [18].

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This ratio Vv/ Vb is referred to as porosity.

$$Vv = Vb – Vt$$

$$\text{Porosity } E = Vb – Vt / Vb = 1- Vt/ Vb$$

Frequently, porosity is expressed as percentage

$$E=100X[1-Vt/Vb]$$

Powder flow properties

One of the ways of measurement of free flowing ability of powder is compressibility.

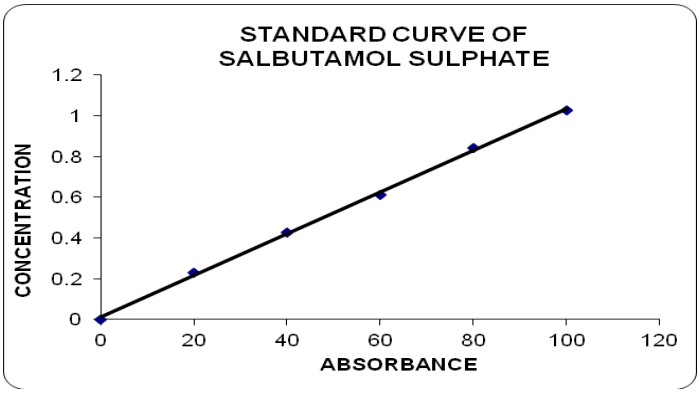
$$\% \text{ Compressibility} = (\rho 1 - \rho 2)/ \rho 1 \times 100$$

Where

ρ1=tapped density,
ρ2=initialbulkdensity13.

Standard Calibration Curve of Salbutamol Sulphate

Solutions ranging from 10 - 100 µg/ml were prepared in distilled water and absorbance was measured at λmax 276 nm using UV Spectrophotometer (ShimadzuUV1700).



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STANDARD CURVE OF SALBUTAMOL SULPHATE

S.NO.	Concentration(µg /ml)	Absorbance
1	0	0
2	20	0.228
3	40	0.428
4	60	0.612
5	80	0.842
6	100	1.028

Evaluation of Tablets

Weight variation

With a tablet designed to contain a specific amount of drug in a specific amount of formula, the weight of a tablet being made is routinely measured to ensure that a tablet contains proper amount of drug15. First weight of 20 tablets was determined. From that average weight was calculated. Then individual tablets were weighed and the individual weight was compared with an average weight.

Hardness and Friability

Using tablet hardness tester, hardness of the tablet was checked. Using Roche Friabilator friability of the tablet was checked. This device subjects tablets to the combined effect of abrasions and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at distance of 6 inches with each revolution. Pre weighed sample of 10 tablets was placed in the Friabilator, which was then operated for 100 revolutions. Tablets were dusted and weighed 16.

The friability was determined using following formula:

$$\text{Friability} = [(\text{Initial weight} - \text{Final weight}) / (\text{Initial weight})] \times 100\ \%$$

Water Absorption Ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation

$$R = 100 \times Wa - Wb / Wb$$

Where, Wb = Weight of tablet before water absorption Wa = Weight of tablet after water absorption.

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***In-vitro* dispersion time**

Tablet was added to 10 ml phosphate buffer solution, pH 6.8 at 37 ± 20^{0}C. Time required for complete dispersion of a tablet was measured

Uniformity of Content

The test is applicable for tablets that contain less than 10 mg or less than 10% w/w of active ingredients. The test for uniformity of content should be carried out only after the content of active ingredient in a pooled sample and tablets has been shown to be within acceptable limits of the stated content. Ten tablets were taken and their content was determined by UV spectrophotometer.

Dissolution Study

Dissolution rate was studied by using USP type II apparatus at 50 rpm using 500 ml of water as dissolution medium at a temperature 37 ± 0.5 ^{0}C as a temperature of dissolution medium. Aliquot of dissolution medium was withdrawn at specific time interval and it was filtered 20. Absorption of filtered solution was checked by UV spectroscopy at 276 nm and drug content was determined from standard calibration curve.

RESULTS AND DISCUSSION:

All the batches were prepared by direct compression techniques using various superdisintegrants in different concentrations as was seen in **(Table 1)**. croscarmellose sodium (CCS), sodium starch glycolate (SSG), Indion 414, were used as super disintegrating agents, microcrystalline cellulose PH-102 was used as diluents, which is also a superdisintegrants.

TABLE . 1 Formulation of Fast dissolving tablets using various super disintegrents

INGREDIENTS (mg)	A1	A2	A3	A4	A5	A6	A7	A8	A9	A10	A11	A12
Salbutamol Sulphate	4	4	4	4	4	4	4	4	4	4	4	4
Indion 414	6	12	18	24								
CCS					6	12	18	24				
SSG									6	12	18	24
Sod. Saccharin	2	2	2	2	2	2	2	2	2	2	2	2
Flavors	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil	2	2	2	2	2	2	2	2	2	2	2	2
Mg. stearate	2	2	2	2	2	2	2	2	2	2	2	2
MCC(PH102)	88	88	88	88	88	88	88	88	88	88	88	88
Mannitol	94	88	82	76	94	88	82	76	94	88	82	76

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TABLE 2: Pre-compression parameters of powder blend

Formulation code	Bulk density (g/cm3)	Tapped density (g/cm3)	Angle of repose (o)	Carr's index (%)	Hausner's Ratio (%)
A1	0.51 ±0.872	0.57 ±1.490	9.74 ±0.426	17±1.51	1.21 ±0.03
A2	0.48 ±1.39	0.55 ±0.175	10.66 ±0.293	15 ± 1.51	1.18 ± 0.04
A3	0.46 ±0.193	0.55 ±0.814	12.47 ±0.945	17 ± 1.20	1.20 ±0.03
A4	0.50 ±0.482	0.57 ±1.50	9.86 ±0.315	15 ± 2.51	1.18 ± 0.03
A5	0.51 ±1.654	0.59 ±0.137	9.4 ±1.121	20 ± 1.58	1.26 ± 0.03
A6	0.49 ±0.859	0.58 ±0.258	12.01 ±1.814	17 ± 1.55	1.21 ± 0.04
A7	0.48 ±1.593	0.57 ±1.663	11.54 ±1.150	17 ± 1.39	1.21 ± 0.04
A8	0.49 ± .722	0.58 ±0.211	12.9 ±0.324	16 ± 2.20	1.20 ± 0.03
A9	0.52 ±0.557	0.60 ±1.034	16.93 ±0.155	16 ± 2.01	1.19 ± 0.03
A10	0.42 ±0.448	0.50 ±0.252	18.08 ±0.486	17 ± 2.12	1.21 ± 0.04
A11	0.43 ±0.253	0.51 ±1.957	15.34 ±1.297	15 ± 1.51	1.18 ± 0.03
A12	0.41 ±0.247	0.49 ±1.882	20.18 ±0.537	17 ± 2.51	1.14 ± 0.03

For each designed formulation, blend of drug and Excipients was prepared and evaluated. As shown in **(Table 2)**, Angle of Repose was found in range of 9.4 to 20.180 while % Bulk density value were ranged in 0.41 ±0.247 to 0.51 ±0.872, Tapped density, which was ranged between 0.49 ±1.882 to 0.57 ±1.490 was found to increase with increase in concentration of superdisintegrants. Also all formulations have shown good flow ability. Tablets were prepared by direct compression technique. Hardness of all tablets was between 2.1-2.5 kg/cm2 while friability and weight variation test result were found within acceptable limits. Also all tablets passed the uniformity of content test as shown in (**Table 3)**. Indion 114 is made by cross-linking (etherification) reaction of Sodium CMC. This cross linking greatly reduces water solubility of Sodium CMC while permitting material to swell and absorbs water many times its weight without losing fiber integrity. Due to this Tablet prepared by using Indion 114 as superdisintegrants were found to have more water absorption ratio and hence in vitro disintegration time for all formulations was very less it was between 25-07 seconds as the concentration is increased as shown in **(Table 3)**.

Table 3: Post- compressional parameters of fast dissolving tablets

Formulation code	Hardness (Kg/cm2)	Friability (%)	Uniformity of Content (%)	Thickness ± SD, n=3	Disintegration Time (Seconds) In vitro	Weight Variation	Amount of drug release (%)
A1	2.5 ± 0.11	0.82 ±0.316	99.22 ±1.261	4.60 ±0.12	25 ±0.256	Passes	102.1 ±1.4
A2	2.3 ± 0.11	0.61 ±0.325	100.08 ±1.431	4.75 ±0.15	14 ±0.426	Passes	101.2 ±1.4
A3	2.2 ± 0.10	0.63 ±0.379	99.86 ±2.194	4.71 ±0.10	08+0.335	Passes	99.64 ±2.7
A4	2.1 ± 0.12	0.61 ±0.548	99.12 ±0.698	4.80 ± 0.10	07 ±0.559	Passes	100.9 ±1.4
A5	2.8 ± 0.18	0.72	100.5 ±2.569	4.85 ± 0.17	26 ±0.365	Passes	100.5

		±0.965					±0.5
A6	2.1 ± 0.10	0.65 ±0.961	100.42 ±1.359	4.87 ± 0.15	20 ±1.154	Passes	99.8 ±1.6
A7	2.1 ± 0.15	0.84 ±0.816	99.88 ±1.246	4.72 ± 0.12	10 ±0.256	Passes	100.6 ±0.8
A8	2.3 ± 0.21	0.72 ±0.246	99.27 ±1.465	4.65 ± 0.09	08 ±0.126	Passes	101.2 ±0.3
A9	2.2 ± 0.10	0.64 ±0.516	99.65 ±1.261	4.61 ± 0.19	12 ±0.123	Passes	100.5 ±0.4
A10	2.3 ± 0.21	0.60 ±0.325	100.08 ±1.431	4.64 ± 0.15	14 ±0.356	Passes	102.1 ±0.6
A11	2.2 ± 0.15	0.70 ±0.349	99.86 ±2.194	4.69 ± 0.14	21 ±0.456	Passes	100.7 ±2.1
A12	2.4 ± 0.15	0.62 ±0.448	100.5 ±0.698	4.73 ± 0.28	25 ±0365.	Passes	99.2 ±0.9

Due to highly porous structure of Croscarmellose sodium, it draws large amount of water by water wicking mechanism into porous network of tablet and thus crospovidone swells very little, yet rapidly absorbs water into its network. Due to this with increase in concentration of Croscarmellose sodium improved water uptake and reduction in disintegration time was observed. It was found that in vitro disintegration time was ranged between 26-08seconds which was not much advantageous than tablets containing Indion 114 as shown in **(Table 3)**.

It was also observed that water absorption ratio of tablet was directly proportional to concentration of sodium starch glycolate. But both in vivo and in vitro disintegration time was increased with increase in concentration of sodium starch glycolate.. Superdisintegrant6 action of sodium starch glycolate is governed by its extensive swelling, which increase with increase in concentration of sodium starch glycolate. Also formations of viscous plugs were observed with increasing concentration of sodium starch glycolate.

So finally it is concluded that formulations containing Indion 414 as super disintegrating agent show rapid in-vitro dispersion time as compared to other formulations.

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