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Formulation and Evaluation of Oral Disintegrating Tablets of Salbutamol Sulfate

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Abstract

Oral fast dissolving drug delivery system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing. Orally disintegrating tablets (ODT) are solid unit dosage forms like conventional tablets, but are composed of superdisintegrants, which help them to disintegrate the tablet rapidly in saliva without the need to take it water. Orally disintegrating tablets (ODT) are not only indicated for people who have swallowing difficulties, but also are ideal for active people. ODT were prepared by using Crospovidone, Sodium starch glycolate and Croscaramellose sodium by direct comparision method. Drug-polymer complex were formulated for drug content and then formulated into oral disintegrating tablets by direct compression method by using different concentrations of superdisintegrants. Tablets were evaluated for weight variation, hardness, thickness, friability, drug content, water absorption ratio, disintegration time, in-vivo and in-vitro drug release. Tablets of F9 formulation containing 6% Crosspovidone and sodium starch glycolate showed faster disintegration within 16.88 seconds. Good correlation was observed between in-vitro and in-vivo disintegration time. Correlation between water absorption and disintegration time showed that thewre exists an inverse relationship between them. In conclusion it was determined that Crosspovidone containing formulation showed better results when compared to others.

Keywords: - *Salbutamol Sulphate, ODT, Super disintegrants*

INTRODUCTION

Oral administration is the most popular route about 50-60% of total dosage forms are administered due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly patient compliance. Solid oral delivery systems do not require sterile conditions and are therefore less expensive to manufacture. One important drawback of solid dosage forms is the difficulty in swallowing (dysphasia) or chewing in some patient's particularly pediatric and geriatric patients.

The problem of swallowing is common phenomenon in geriatric patient due to fear of choking, hand tremors, dysphasia and in children's due to underdeveloped muscular and nervous systems and in schizophrenic patients resulting in poor compliance with oral tablet drug therapy which leads to reduced overall therapy effectiveness. Difficulties in swallowing of tablet and capsule also occur when water is not available, in diarrhea, coughing during the common cold, allergic condition and bronchial infection.

Oral fast dissolving drug delivery system (OFDDS) is one such novel approach to increase consumer acceptance by virtue of rapid disintegration, self-administration without water or chewing (Suresh Bandari et al., 2008).

Orally disintegrating tablets (ODT) are solid unit dosage forms like conventional tablets, but are composed of superdisintegrants, which help them to disintegrate the tablet rapidly in saliva without the need to take it water. Orally disintegrating tablets (ODT) are not only indicated for people who have swallowing difficulties, but also are ideal for active people.

United States Food and drug administration (FDA) defined ODT as "a solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." Orally disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet (Parakh S. R et al., 2003).

Recently European pharmacopoeia also adopted the term 'orodispersible tablet' as a

tablet that is to be placed in the mouth where it disperses rapidly before swallowing. Despite various terminologies used, orally disintegrating tablets are here to offer unique form of drug delivery with many advantages over the conventional dosage forms.

The US Food and Drug Administration 2008 publication of guidance for industry: Orally Disintegrating Tablets. Three main points stand out in the final guidance (Rakesh Pahwa et al., 2010):

1. ODTs should have an *In vitro* disintegration time of approximately 30 s or less (using United States Pharmacopeia disintegration test or equivalent).

2. Generally, the ODT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an ODT for both patients and regulators.

The guidance serves to define the upper limits of the ODT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an ODT.

MATERIALS AND METHODOLOGY

Materials

Salbutamol sulfate was gifted from Yashica Pharmaceuticals, Crosspovidone, Cross caramellose sodium Sodium Starch Glycolate, MCC (Avicel PH 102), Magnesium Sterate, Aspartame, Orange flavor are from Hetero Drugs, Hyd, Mannitol (D-Mannitol) were purchased from Qualikems Fine Chem Pvt. Ltd.

Methods

Preparation of Salbutamol sulfate ODTs by direct compression technique

Salbutamol sulfate ODTs were prepared using direct compression technique. Direct compression technique is a convenient method.

Different formulations of Salbutamol sulfate ODTs were designed to be prepared by direct compression technique using three disintegrants (Crosspovidone, Crosscaramellosesodium, Sodium starch glycolate). Disintegrants is varied with 3 different concentrations (i.e., 2, 4 and 6 % respectively) keeping all other ingredients constant, there are assigned with formulations codes shown in table.

Table 1: Formula of Salbutamol sulfate Oral Disintegrating Tablets prepared by Direct Compression Method

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Salbutamol sulfate	4	4	4	4	4	4	4	4	4
Sodium starch glycolate	2	4	6	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	2	4	6	-	-	-
Crosspovidone	-	-	-	-	-	-	2	4	6
MCC pH 102	28	26	24	28	26	24	28	26	24
Mannitol	58	58	58	58	58	58	58	58	58
Aspartame	5	5	5	5	5	5	5	5	5
Sodium stearyl fumarate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Aerosil	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5
Spearmint flavor	2	2	2	2	2	2	2	2	2

water absorption ratio.

Procedure

Drug, disintegrants, micro crystalline cellulose, mannitol and flavor were accurately weighed and through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15minutes.The obtained blend was lubricated with sodium steary lfumarate and aerosil and mixing was continued for further 5minutes. The resultant mixture was directly compressed into tablets by using 6mm round concave faced punch of rotary tableting machine. Compression force was kept for all formulations.

Evaluation of orally disintegration tablet formulations

Different quality control tests were performed for all the ODT formulations to check whether these have met the specifications given in USP along with other *In vitro* tests like wetting time and

Various *In vitro* tests performed are

- Weight variation test
- Thickness measurement
- Hardness and Friability
- Assay
- Wetting time
- Water absorption ratio
- Disintegration Time and
- Dissolution test

Weight variation test

Method 20 tablets were randomly selected from each formulation and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight. The Mean ± S.D. were noted. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit and if

no tablet differs by more than 2 times the percentage limit.

Thickness measurement

Method: 10 tablets were taken from each formulation and their thickness was measured using a digital screw gauge. The individual tablet was placed between two anvils of the screw gauge and sliding knob was rotated until the tablet was tightly fitted. The digital reading displayed was noted. The Mean ± S.D. were noted. The tablet thickness should be controlled within a ± 5% variation of standard value.

Hardness

The tablet hardness of different formulations was measured using the Monsanto hardness tester. The tester consists of a barrel containing a compressible spring held between two plungers. The lower plunger was placed in contact with the tablet, and a zero was taken. The upper plunger was then forced against the spring by turning a threaded bolt until the tablet fractures. As the spring is compressed, a pointer rides along a gauge in the barrel to indicate the force. The force of fracture is recorded, and the zero force reading is deducted from it. Generally, a minimum hardness of 4 kg is considered acceptable for uncoated tablets. The hardness for ODTs should be preferably 1-3 kg.

Friability

This test is performed using a laboratory friability tester known as Roche Friabilator. 10 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25 rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated.

$$\% \text{ Friability} = \frac{(w1 - w2)}{w1} \times 100$$

Where,

W1 = Initial weight of the 20 tablets before testing.

W2 = Final weight of the 20 tablets after testing.

Friability values below 1% are generally acceptable.

Assay

20 tablets were randomly selected, weighed and finely powdered and quantity of powder equivalent to one tablet was added to 100 ml solvent of pH 6.8 phosphate buffer in a conical flask.

Conical flasks were placed on a rotary shaker overnight. An aliquot of solution was centrifuged and supernatant was filtered through a 0.22µ filter. Absorbance of the resulted supernatant solution was measured using U.V Visible spectrophotometer at a wavelength of 278nm against pH 6.8 phosphate buffer as blank. Concentrations were calculated with the help of standard graph and total amount present in the formulation was calculated.

Wetting time and Water absorption ratio *(R)*

Method: Five circular tissue papers were placed in a petri dish with a 10 cm diameter. Ten milliliters of water containing eosin, a water-soluble dye, was added to the petri dish. The dye solution is used to identify the complete wetting of the tablet surface. A tablet was carefully placed on the surface of tissue paper in the Petri dish at room temperature. The time required for water to reach the upper surface of the tablets and completely wet them was noted as the wetting time. To check for reproducibility, the measurements were carried out in replicates (n=6). The wetting time was recorded using a stopwatch.

The weight of the tablet before keeping in the Petri dish was noted (W_b) using Shimadzu digital balance. The wetted tablet from the Petri dish was taken and reweighed (W_a) using the same. The Water absorption ratio, R, was determined according to the following equation:

$$R = 100 (Wa - W_b) / W_b$$

Where W_b and W_a are the weight before and after water absorption respectively.

Disintegration Time

Disintegration time is considered to be one of the important criteria in selecting the best formulation. To achieve correlation between disintegration time *In vitro* and *In vivo* (in oral cavity) several methods were proposed, developed and followed at their convenience. One of the simple methods followed is described below.

Method: Disintegration time was also measured using a modified disintegration method (n=6). For this purpose, a Petri dish (10 cm diameter) was filled with 10 ml of water. The tablet was carefully put in the center of the Petri dish and the time for the tablet to completely disintegrate into fine particles was noted using a stop watch.

Dissolution test

Method: Dissolution test was carried out using USP rotating paddle method (apparatus 2). The stirring rate was 50 rpm. 6.8 pH phosphate buffer was used as dissolution medium (900ml) and was maintained at 37 ± 1^0C. Samples of 5ml were withdrawn at pre – determined intervals (2, 4, 6, 8, 10, 15, 20, 25, 30 min), filtered and replaced with 5ml of fresh dissolution medium. The collected samples were suitably diluted with dissolution fluid, where ever necessary and were analyzed for the salbutamol sulfate at 278 nm by using UV spectrophotometer. Each dissolution study was performed for three times and mean values were taken.

RESULTS

Table 2: Preformulation characteristics of Salbutamol sulfate Oral Disintegrating tablets

Formulation Code	Bulk density(g/cc)	Tapped density(g/cc)	Hausner's ratio	Compressibility index (%)	Angle of repose (θ)
F1	0.425±0.15	0.527±0.25	1.19±0.16	16.75	28.98
F2	0.428±0.35	0.514±0.27	1.20±0.30	17.37	30.21
F3	0.429±0.22	0.521±0.29	1.28±0.22	18.46	30.19
F4	0.413±0.16	0.512±0.21	1.25±0.16	17.60	28.43
F5	0.417±0.37	0.515±0.28	1.22±0.26	18.71	30.35
F6	0.433±0.16	0.509±0.24	1.20±0.21	16.26	30.20
F7	0.423±0.24	0.519±0.30	1.20±0.25	18.32	28.12
F8	0.419±0.30	0.515±0.28	1.28±0.23	19.08	29.17
F9	0.411±0.28	0.509±0.29	1.24±0.22	18.44	28.17

Table 3: Formulation characteristics of Salbutamol sulfate Oral Disintegrating tablets

a: Mean ± S.D., n=6 tablets, b: Mean ± S.D., n=10, c: Mean ± S.D., n=20

Formulation	Weight(mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Drug content (%)
F1	98.26±0.62	2.22 ±0.10	2.76±0.30	0.59	99.46±0.45
F2	99.41±0.59	2.22±0.12	2.68±0.23	0.65	99.01±0.56
F3	98.08±0.61	2.19±0.09	2.75±0.21	0.58	99.11±0.25
F4	99.29±0.67	2.18±0.11	2.55±0.46	0.68	99.15±0.65
F5	100.04±0.39	2.19±0.16	2.82±0.42	0.41	99.20±0.25
F6	99.25±0.52	2.18±0.14	2.87±0.56	0.47	98.85±0.49
F7	99.25±0.45	2.19±0.10	2.73±0.36	0.56	98.31±0.42
F8	98.75±0.28	2.12±0.05	2.82±0.40	0.45	98.96±0.57
F9	98.91±0.59	2.17±0.07	2.68±0.39	0.58	99.31±0.29

Table 4: Formulation characteristics of Salbutamol sulfate Oral Disintegrating tablets

Formulation Code	Disintegrating time	Wetting time	Water absorption time	In vitro dispersion time(sec)
F1	26.26±0.61	36.45±0.24	62.25±0.87	27.65±0.25
F2	22.23±0.39	42.12±0.15	75.18±0.24	24.21±0.11
F3	20.54±0.44	30.11±0.57	79.23±0.12	20.46±0.26
F4	28.27±0.29	38.41±0.25	56.25±0.44	29.25±0.57
F5	24.57±0.12	34.44±0.32	67.21±0.22	26.55±0.80
F6	21.88±0.98	33.38±0.21	73.23±0.49	25.69±0.27
F7	22.27±0.49	35.23±0.51	45.56±0.29	32.49±0.78
F8	20.57±0.56	31.47±0.28	53.81±0.11	30.17±0.65
F9	16.88±0.88	27.48±0.57	63.52±0.14	26.44±0.71

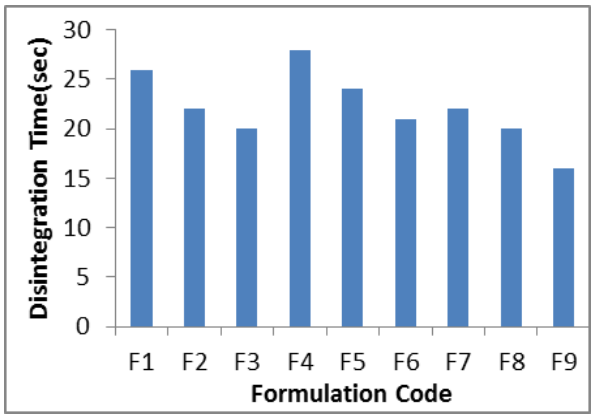

Fig. 1.1: Disintegration

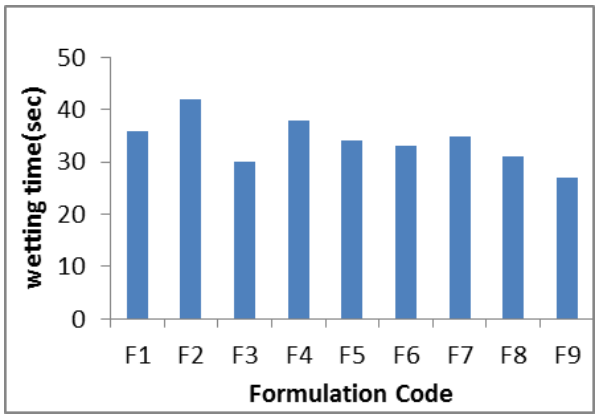

Fig. 1.2: Wetting time

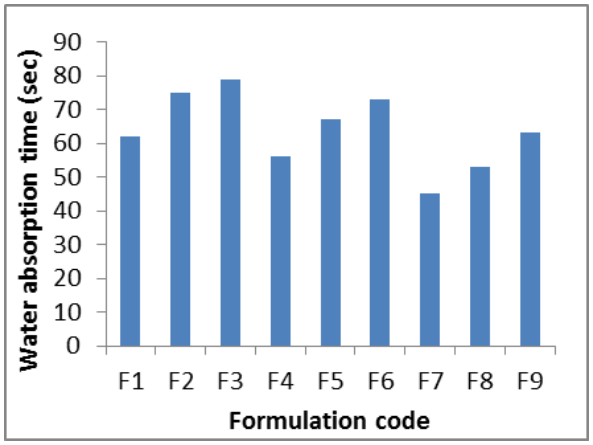

Fig. 1.3: Water absorption time

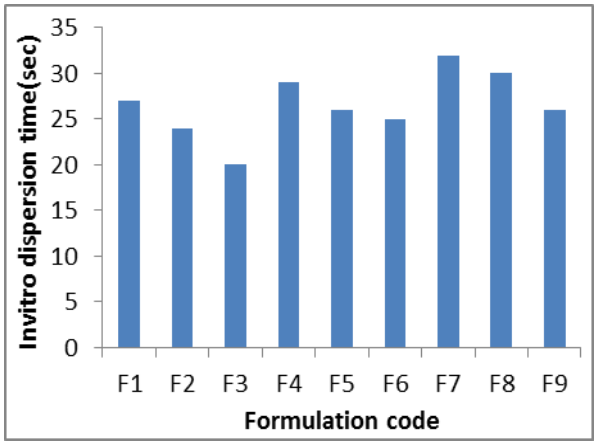

Fig. 1.4: In vitro dispersion time

Figure 1: Graphical representation of Salbutamol sulfate Oral Disintegrating Tablets

DISSOLUTION STUDIES

Table 5: Cumulative percent Salbutamol sulfate released from ODTs containing varying concentrations of different super disintegrating agents

TIME (mins) & FORMULATION CODE	2	5	10	15	20	25
F1	25.02±0.51	42.34±0.15	49.81±0.05	67.56±0.09	82.21±0.51	99.62±0.39
F2	27.84±0.09	49.81±0.30	58.74±0.07	72.27±0.27	84.17±0.34	99.47±0.37
F3	31.74±0.09	57.19±0.10	70.78±0.08	83.65±0.13	92.02±0.35	99.51±0.10
F4	21.39±0.43	38.52±0.12	45.99±0.27	60.99±0.13	76.83±0.22	99.31±0.14
F5	22.59±0.17	44.95±0.11	56.67±0.38	72.47±0.24	81.33±0.19	99.27±0.21
F6	27.31±0.17	52.06±0.30	63.35±0.31	79.02±0.18	90.24±0.52	99.32±0.21
F7	28.26±0.18	47.61±0.19	56.36±0.10	72.33±0.32	85.86±0.27	99.92±0.16
F8	31.74±0.20	52.53±0.10	62.28±0.17	87.31±0.11	92.76±0.28	98.13±0.21
F9	34.87±0.17	63.22±0.31	75.37±0.11	97.98±0.39	99.98±0.13	-

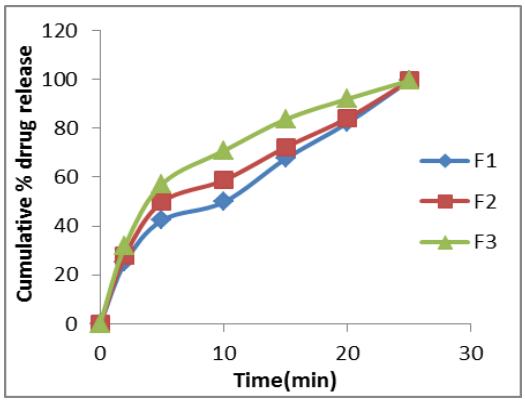

Fig. 2.1: %Cummulative drug release of sodium starch glycolate as super disintegrant

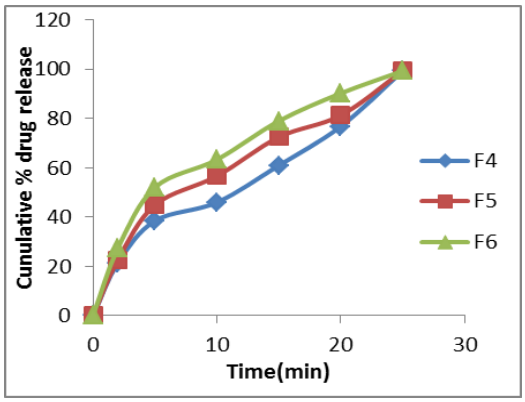

Fig. 2.2: %Cummulative drug release of cross caramellose as super disintegrant

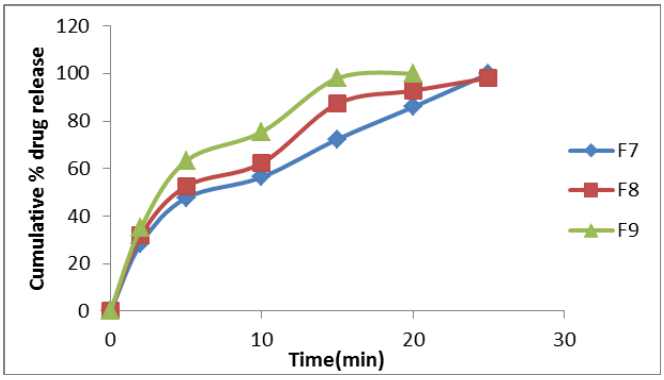

Fig. 2.3: % Cumulative drug release of cross povidone as super disintegrant

Figure 2: Graphical representation of cumulative % drug release of Salbutamol sulfate Oral Disintegrating Tablets prepared individually varying concentrations of super disintegrating agents.

DISCUSSION

Using various disintegrants like Crospovidone, Croscaramellose sodium and Sodium starch glycolate tablets were prepared along with other additives. Direct compression method was used for the preparation of tablets. A total number of 09 formulations were prepared and evaluated.

To achieve rapid disintegration time, most of the excipients selected must be water soluble by nature. This excipient was used a bulking agent to achieve the desired tablet weight. Microcrystalline cellulose 102 was included in the formulation mainly as a disintegrant at the concentrations used and to some extent as diluents. This grade of microcrystalline cellulose is powder in nature and thus displays excellent flow. To impart pleasant taste and mouth feel Aspartame and Spearmint were included as sweetening and flavoring agents respectively. Sodium stearyl fumarate was employed as a lubricant instead of magnesium stearate to overcome the metallic taste of the latter and also due to its water soluble nature.

Crospovidone polymers are densely crosslinked homopolymers of N – vinyl 2 – pyrrolidones. Their porous particle morphology helps to rapidly wick liquids into the tablet by capillary action to generate the rapid volume expansion and hydrostatic pressures that cause tablet disintegration. In addition to its unique particle size and morphology, crospovidone is nonionic and its disintegration performance will neither be influenced by pH changes in the gastrointestinal tract nor will they complex with ionic drug actives. They can also be used as solubility enhancers resulting in a faster dissolution rate without forming gels.

Croscarmellose sodium is crosslinked carboxymethyl cellulose sodium which can be used at concentrations of upto 5% as a disintegrant. Its unique fibrous nature gives excellent water wicking capabilities and crosslinking makes it hydrophilic and highly absorbent material, resulting in its swelling properties. It rapidly swells upto 4 – 8 times its original volume on contact with water. Like crospovidone, it is also used as a dissolution aid, hence the name Ac-Di-Sol (accelerates dissolution).

Sodium starch glycolate is a sodium salt of carboxymethyl ether of starch,usually employed at concentrations between 2 – 8% although an optimum concentration of 4% may sufficient in many cases. Disintegration occurs by rapid uptake of

water followed by rapid and enormous swelling, which is its primary mechanism of action. It (explotab) swells upto 300 times its original volume in water.

Pre-formulation studies

The results obtained by evaluating the powder blends of drug and excipients are shown in table. Bulk density and tapped density were found in the range of 0.411 – 0.433 g/cc and 0.509 – 0.527 g/cc respectively. The value of Hausner Ratio was in between 1.19 – 1.28 (< 1.28) indicating that all batches of powder blends were having good compressibility. Values of angle of repose (θ) was found in the range of 28.12 – 30.35 showing that blend of powder was free flowing and can be used for direct compression.

Weight variation and Thickness

In all formulations, tablet weight and thickness were within mean ±9.5% and mean ±5% respectively. The average weight in all the nine formulations was found to be 98.08±0.61mg to 100.04±0.39mg. The thickness varies between 2.12±0.05 to 2.22±0.12 mm.

Friability and Hardness

Friability values were less than 1% in all cases. Hardness of all the tablets was maintained at 2.55±0.46 to 2.87±0.56 kg/cm^2 for all the formulations as mentioned before. Assay was performed and percent drug content of all the tablets were found to be between 98.31±0.42% and 99.46±0.45% of Salbutamol sulfate, which was within the acceptable limits.

Wetting time

Wetting time was determined for all the formulations. The values lie between 21.76 ± 0.75 to 39.53 ± 0.18sec. The variability in wetting time for different formulations may be due to the changes in the compaction which cannot be controlled during tablet preparation and the type of the disintegrant affected the wetting of the tablets. On comparing the disintigrants the formulations containing crospovidone and pre gelatinized starch and sodium starch glycolate take less wetting time than the other formulations.

Water absorption ratio

Water absorption ratio ranged from 55.30 ± 0.61 to 76.80 ± 0.15%. Crosspovidone and Croscarmellose sodium perform their disintegrating action by wicking through capillary action and fibrous structure, respectively with minimum gelling. The relative ability of the various disintegrants to wick water into the tablets was studied. After contact with water the tablets containing sodium starch glycolate

swelled, the outer edge appeared gel like. Tablets containing crosspovidone quickly wicks water and were hydrated, but were soft as compared with tablets prepared with pre-gelatinized starch and sodium starch glycolate. The center of the tablets with sodium starch glycolate and pre-gelatinized starch remained dry and hard.

Disintegration time

Disintegration time is considered to be important criteria in selecting the best ODT formulation. The *in vitro* disintegration time for all the 09 formulations varied from 16.88±0.88 to 28.27±0.29 seconds. The rapid disintegration was seen in the formulations containing Crosspovidone and formulations containing combination of disintegrants (CP + CCS, PGS + SSG). This is due to rapid uptake of the water from the medium, swelling and burst effect.

It is also noticed that as the disintegrant concentration was increased from 3% to 8% the time taken for disintegration was reduced. The disintegration time of formulation (F9) was found to be lower (16.88 ± 0.88) and was selected as the best ODT formulation among all the 09 formulations.

In vitro dispersion

In vitro dispersion is a special parameter in which the time taken by the tablet for complete dispersion is measured. The time for all the 09 formulations varied between 20.46±0.26 to 32.49 ± 0.78 sec.

In vitro dissolution

The development of dissolution method for ODTs is almost similar to the approach taken for conventional tablets until they utilize the taste masking. The taste masking aspect greatly influences dissolution method development, specifications, and testing. Several factors like varied thickness and pH dependent solubility of drug particle coating influence dissolution profiles of ODTs containing taste masked actives. Since Salbutamol sulfate is bitter in taste, the bitter taste of drug was masked by using polymers, sweeteners and flavors. It has been reported that USP type II apparatus with a paddle speed of 50 rpm is commonly used for ODT formulations. Slower paddle speeds are utilized to obtain good profiles as these formulations disintegrate rapidly.

In vitro dissolution studies of the prepared ODTs was performed in mixture of solvent P^H 6.8 phosphate buffer using USP dissolution apparatus type 2. The

dissolution rate was found to increase linearly with increasing concentration of disintegrants. Formulations F1, F2 and F3 which contained increasing concentrations of Sodium starch Glycolate have recorded drug release 99.62 ± 0.39%, 99.47 ± 0.37% and 99.51 ± 0.10% respectively within 25 min. Formulations F4, F5 and F6 which contained increasing concentrations of Caramellose sodium have recorded drug release 99.91 ± 0.14%, 99.32 ± 0.21% and 99.32 ± 0.21% respectively, at the end of 25 min. Formulations F7, F8 and F9 which contained increasing concentrations of Crosspovidone have recorded drug release 99.92 ± 0.16%, 98.13 ± 0.21% and 100 % respectively, at the end of 25 min.

Drug content

Assay was performed and percent drug content of all the batches were found to be 104.19 ± 0.71, 99.40 ± 0.74 and 101.82 ± 0.15 of Salbutamol sulfate, which was within the acceptable limits.

CONCLUSION

Salbutamol Sulfate ODT tablets was developed by using various concentrations of different superdisintegrating agents (Sodium Starch Glycolate, Crospovidone & Croscaramellose) to dissolve/disintegrate very fastly when placed in the mouth by using direct compression method. The results were indicating a promising potential of the Salbutamol Sulfate ODT tablet has given more percentage drug release and fast disintegration in Crospovidone (F9 with 6%concentration) used as superdisintegrant compared to other superdisintegrants.

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