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DEVELOPMENT AND CHARACTERIZATION OF ORAL DISINTEGRATING MINI - TABLET CONTAINING SALBUTAMOL SULPHATE BY SUBLIMATION METHOD

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ABSTRACT

In pharmaceutical industry oral drug delivery is presently regarded as the most accepted route. But the main drawback of the oral dosage forms like delayed on set of action, difficulty in swallowing and poor patient compliance. The aim of the present investigation was to develop and evaluate the oral disintegrating mini-tablet (ODMT) of Salbutamol sulphate by sublimation method for the treatment of Asthma and Chronic pulmonary diseases (COPD). Immediate release tablets are highly accepted because rapid release drug delivery systems and thus, an attempt was made to improve the lag time, bioavailability and patience compliance. To reach this goal three different superdisintegrants were used namely Crospovidone, Sodium starch glycolate, and Croscarmellose Sodium used in different concentration (3 and 9%). Along with camphor used as a sublimating agent. Miromeritic properties of the powder blend were well within the limit confirmed by having good flow property and FTIR and DSC studies confirm the compatibility between drug and excipients and post formulation parameters were evaluated. Among the formulations F2 resulted a least disintegration and dissolution studies hence concluded that ODMTs give better effect to the asthma and COPD patients to improve the lag time, better patient compliance.

KEYWORDS: Oral disintegrating tablets**,** Salbutamol sulphate, Superdisintegrants, Sublimation method.

INTRODUCTION

Despite of enormous innovative in drug delivery, solid dosage form play a vital role among all pharmaceutical dosage form. Oral delivery presently considered as safe and most convenient method of drug delivery. Tablet are mainly used as solid dosage form, the problem associated in conventional tablets like difficulty in swallowing and poor patient compliance.[1]

The problem associated with the conventional tablet can be overcome by Oral disintegrating tablet (ODT) are the new solid dosage form which disintegrates fastly in tongue, usually within a few seconds without need of water. [2]

ODTs are also called as "Orodispersible, Fast dissolving tablets (FDTs), porous tablets, rapid dissolving tablet, Crunch- melt tablet, and bite dispersible tablets".[3]

Mini tablets represent a novel in solid dosage form, it is possible to produce different kinds of mini-tablets like Pediatrics mini-tablets, Bio-adhesive mini-tablets, pH responsive mini-tablets, extended release formulation, Biphasic mini-tablets, gastrointestinal tract, orally disintegrating mini-tablets (ODMTs).[4] For pediatric patients ODMTs is more suitable and substitute to conventional oral dosage forms. It offers various advantages such as better feel mouth, accurate dose, and improved stability, compared to oral liquids. The big challenges occur during formulation of liquids are to mask the bitter taste of the drug, bulkiness, reduced stability, and incompatibilities. This problem overcome by oral disintegrating mini tablets have been projected as a novel method of oral drug delivery.[5]

Asthma is simply described as respiratory disorder that influence respiratory tract , characterized by attack of Coughing, wheezing ,breathlessness and tight chest which are trigger by the respiratory tract becoming inflamed and narrowed. Salbutamol sulphate is a β_2 receptor agonist generally used as drug of choice as an Asthma and Chronic obstructive pulmonary diseases (COPD) patients.The main goal of present study was to develop the fast dissolving tablets taking Salbutamol sulphate as a medicament to decrease the lag time and providing quick onset of action to relieve the asthma and COPD patients. From this study subliming agent is used to intensify the porosity of the tablets.[6]

MATERIALS AND METHODS

Materials

Salbutamol sulphate was obtained from SM pharmaceuticals Bengaluru, India. Camphor was obtained from Thomas baker Pvt.ltd, Mumbai, India.

Crospovidone, Croscarmellose Sodium and sodium starch glycolate were obtained from Shreeji chemicals (Mumbai, India). Magnesium stearate, microcrystalline cellulose, Talc and Mannitol were procured from S. D. Fine chemicals Pvt. Ltd, Mumbai. All other reagents used were of analytical grade.

METHOD

PREPARATION OF ORAL DISINTEGRATING MINI- TABLETS

Orally disintegrating mini-tablet of Salbutamol sulphate were prepared using different concentration of superdisintegrants (3 and 9%) by Sublimation method. All the ingredients were weighed and passed through sieve 60 # screen prior to mixing and transferred into mortar and triturated well. The resulting mixture was compressed into 100mg tablets. These tablets were dried at 60˚C oven till constant weigh obtained.The detailed composition of the formulation is shown in table 1.[7]

Table 1: Formulation details of oral disintegrating mini-tablet tablet of salbutamol sulphate.

SI. No	INGREDIENTS (mg\tab)	F1	F2	F3	F4	F5	F6
1	Salbutamol sulphate	2	2	2	2	2	2
2	Camphor	4	4	4	4	4	4
3	Microcrystalline cellulose	35	35	35	35	35	35
4	Crospovidone	3	9	-	-	-	-
5	Croscarmellose Sodium	-	-	3	9	-	-
6	Sodium starch glycolate	-	-	-	-	3	9
7	Mannitol	53	47	53	47	53	47
8	Talc	2	2	2	2	2	2
9	Magnesium sterate	1	1	1	1	1	1

PREFORMULATION TEST

1. Angle of repose(θ)

The attritional force in a loose powder can be measured by angle of repose. It is defined as the maximal angle possible between the surface of a heap of the powder and horizontal plane. It was studied by using fixed funnel method.

$$\theta = tan - 1(h/r)$$

2. Bulk density

Weighed the amount of the blend previously passed through sieve and transferred in measuring cylinder and carefully passed level of the powder without compacting, bulk volume was measured, it results the initial and final volume was calculated using formula.

$$BD = M/Vb$$

3. Tapped density

The total mass of the blend was poured into graduated cylinder it was tapped for fixed time using mechanically tapped density tester, then initial and final volume was noted by using the formula.

$$TD = M/Vt$$

4. Carr's index

It is indication of flow ability, cohesiveness and compressibility properties of the drug and excipient powder blend, then it was calculated by using the formula.

$$Carr's\ index = \frac{TD - BD}{TD} X\ 100$$

5. Haunser's ratio

It is defined as flow properties of powder blend and It is the ratio of tapped density to bulk density and This can be calculated by using formula. [8] [9]

$$Hausner's\ Ratio = \frac{TD}{BD}$$

Table 2: Characterization of powder blend.

Code	Angle of repose (°) (±SD*)	Bulk density(g/cc) (±SD*)	Tapped density(g/cc) (±SD*)	Carr's index (%) (±SD*)	Haunser's ratio (±SD*)
F1	21.58±0.82	0.481±0.080	0.501±0.019	15.71±3.25	1.14±0.055
F2	21.14±0.62	0.482±0.082	0.514±0.022	15.84±2.57	1.12±0.051
F3	20.60±0.58	0.484±0.087	0.518±0.025	14.82±2.41	1.15±0.056
F4	20.30±0.52	0.480±0.086	0.526±0.029	15.92±3.28	1.14±0.055
F5	21.96±0.78	0.464±0.068	0.482±0.035	14.85±2.48	1.13±0.052
F6	21.11±0.65	0.473±0. 084	0.495±0.031	13.91±0.98	1.16±0.06

*represented as mean ±SD, n=3.

EVALUTIONS

The Salbutamol sulphate oral disintegrating mini-tablet evaluations for the following parameters.

1. Fourier transforms infra-red spectroscopy (FT-IR) studies

By using Shimadzu FT-IR-8400s spectrophotometer (Japan) to known the compatibility between the pure drug and also physical mixture utilized in the formulation of oral disintegrating tablet .The frequency range was from 400 to 4000 cm $^{-1}$ Samples were prepared in KBr press pellet technique.

2. Differential scanning calorimetric (DSC)

The DSC examination of pure drug salbutamol sulphate and physical mixture was tested using Shimadzu DSC-60 (PerkinElmer, USA) calorimeter. The temperature range10°C to 300°C and at the speed of 5.00 °C min $^{-1}$ under the nitrogen flow of 25ml min^{-1} finally thermograms were recorded. [10]

3. Weight variation

Formulated oral disintegrating mini-tablet were carried out for uniformity of weight, 20 tablets were weighed individually and collectively. The percent (%) weight variation test was calculated by using the formula. [11]

%Weight variation= (Average weight)-(Individual weight)/ (Average weight) X 100.

4. Tablet hardness

Tablet hardness is tensile strength of tablet it was determined by using hardness tester. Commonly expressed in kg/cm^2**.**

5. Friability

Friability is the loss of weight of tablet in the package/container, due to removal of fine particles from the surface. From each batch ten tablets were selected it was placed in friabilator. The drum was operated for 25rpm for 4 minutes (100 revolutions). The tablets were dusted and again weighed then the percentage of friability was calculated by using the formula. [12]

$$\% \text{ Friability} = \frac{\text{Initial weight of tablets} - \text{Final weight of tablets}}{\text{Initial weight of tablets}} \text{ X } 100$$

6. Drug content uniformity

Oral disintegrating mini-tablet were crushed and the powder blend is equivalent to drug. By using the UV spectrometer the absorbance was analysed.[13]

7. *In-vitro* disintegration test

The *in-vitro* disintegration of oral disintegrating mini-tablet was carried out using conventional disintegration apparatus for complete disintegration of sublingual-tablets. From each batch six tablets was placed in the test apparatus time is required until complete disintegration of each batch, which in turn made it possible to compare the disintegration time of different batches.[14]

8. Wetting time test

The test was evaluated by use of petridish plate containing water along with dye solution. The tablet is placed on the centre of petridish, then time is noted as a wetting time.[15]

9. *In-vitro* dissolution studies

In -vitro drug release for the drug was carried out using USP-2 dissolution apparatus. The speed of the apparatus was 100 rpm, commonly maintained temperature 37±0.5 ^{0}C, 900ml phosphate buffer (6.8 pH) is used. Tablets was introduced into dissolution flask, after certain interval of time the sample was withdrawn and absorbance was analysed using UV spectrometer. [16]

10. Acelerated stability studies

Optimized ODMTs of salbutamol sulphate was kept at 40 ± 2^{0}C with 75 ± 5% RH for a period of 3 months as per ICH guidelines. The physical condition and drug content, wetting time, dissolution, and disintegration were analysed.

Table 3: Evalution parameter of Salbutamol sulphate ODMT.

Code	Hardness (Kg/cm^2) (±SD*)	Friability (%) (±SD$^\alpha$)	Weight variation (mg) (±SD$^\alpha$)	Wetting time (sec) (±SD$^\beta$)	Disintegration time (sec) (±SD$^\beta$)	Drug content uniformity (%) (±SD*)
F1	1.73±0.02	0.14±0.01	100.12±0.23	5.26±0.078	19.2±0.18	97.69±0.13
F2	1.92±0.01	0.12±0.02	100.56±0.52	3.56±0.126	12.8±023	98.54±0.10
F3	1.82±0.15	0.24±0.03	101.65±0.25	4.10±0.065	15 .2±0.08	95.56±0.11
F4	1.9±0.005	0.20±0.03	102.39±0.12	10.5±0.081	38.57±030	94.74±0.08
F5	1.85±0.01	0.12±0.02	100.45±0.35	18.2 ±0.1	23.35±0.16	94.57±0.03
F6	1.91±0.01	0.22±0.03	100.29±0.19	20.2±0.01	52.35±0.21	93.63±0.07

*represented as mean ±SD, n=3.

$^\alpha$ represented as mean ±SD, n=10.

$^\beta$represented as mean ±SD, n=6.

Table 4: Accelerated stability testing of optimized formulation.

Temperature and RH	Parameters	Duration in months			
		0	1	2	3
40±2˚C and 75±5%	Wetting time	3.56	2.65	2.60	2.50
	Disintegration time	12.8	13.0	12.9	12.2
	%Drug content	98.54	98.45	98.27	97.98
	%CDR	96.48	95.35	95.21	94.96

RESULT AND DISCUSSION

The present work orally disintegrating mini-tablet (ODMTs) of Salbutamol sulphate were prepared using different concentration (3 and 9%) of super disintegrants by Sublimation method. FTIR and DSC of the pure drug and physical mixture revealed that there is no interaction between drug and the polymers. Miromeritic properties of the powder blend were well within the acceptable limit confirmed by free flowing were recorded in the table 2. After compression of tablets were subjected to post formulation of tablets. Prepared tablets were found within the hardness range 73±0.026 to 1.92±0.01 Kg/cm^2 formulation shows the good mechanical strength and transportation. All the tablets passed the weight variation test and were found to be in the acceptable limit according to USP (± 10). Friability values for all the batches were in the range of less than 1% indicating that an acceptable limit. According to USP the formulations should disintegrate completely within one minute which shows faster disintegration. The wetting time range of all batches was found to be in the range 3.56±0.126 to 20.2±0.01 sec. The percent drug content for all the formulations were calculated by measuring the absorbance at 276 nm was found to be in the range of 93.63±0.07% to 98.54±0.10 % with an acceptable limit based on USP.

Comparative *in-vitro* drug release value of formulation F1 to F6

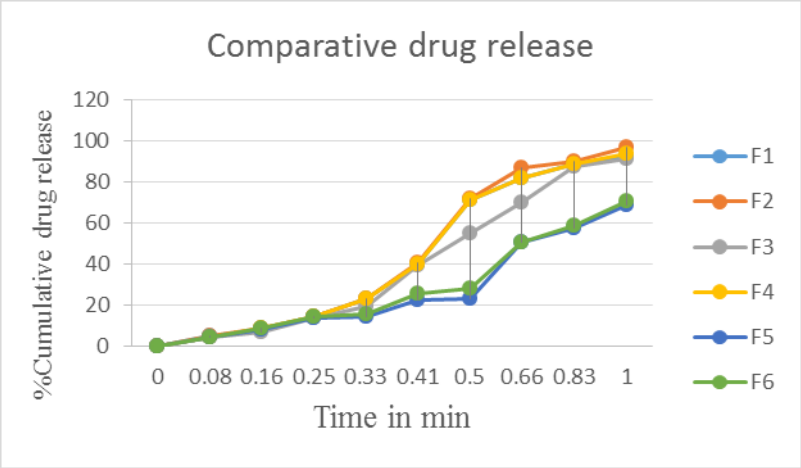

Fig.no:1 Comparative *in-vitro* drug release profile of Salbutamol sulphate for formulations F1 to F6.

The %Cumulative drug release for all the formulation (F1 to F6). The formulations showed an average range drug release at the end of one minutes. Figure illustrates the comparative in-vitro drug release profile for Salbutamol sulphate for formulations F1 to F6. From the dissolution studies exhibits the drug release patterns were found to be in range 68.65%- 96.48%. Among the formulations observed that crospovidone shows more drug release than other formulations.

Stability studies

Stability studies for F2 formulation (optimized formulation) reveals that there is no changes hence concluded there is no physical and chemical parameters hence concluded that F2 formulation stable for 3 months.

CONCLUSION

In the present work it concluded that the oral disintegrating mini- tablet containing Salbutamol sulphate by using superdisintegrants such as Crospovidone, Croscarmellose Sodium and Sodium starch glycolate at different concentration (3 and 9%) formulated by sublimation method using camphor used as a sublimating agent. Pre formulation and post formulation were evaluated. All the results were found well within the acceptable limits. Among the formulations F2 showed good results with least disintegration time of 12.8±023sec with higher drug release at 96.48%. Hence concluded that the optimized formulations improved the lag time, better patient compliance and providing fast onset of action to relief the asthma and COPD patients.

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